UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: September 14, 2016

SUBJECT: d-Phenothrin Draft Human Health Risk Assessment for Registration Review

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Petition No.: N/A	**Regulatory Action:** Reregistration
Risk Assessment Type: N/A	**Case No.:** 0426
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FROM: Jessica Kidwell, Risk Assessor
Abdallah Khasawinah, PhD., Toxicologist
Ivan Nieves, ORE Assessor
Wade Britton, MPH, Environmental Health Scientist
Dennis McNeilly, Residue Chemistry and Dietary Exposure Assessor
Risk Assessment Branch 4
Health Effects Division (7509P)

THROUGH: Elissa Reaves, Ph.D., Branch Chief
Risk Assessment Branch 4
Health Effects Division (7509P)

Kelly Lowe
Sheila Piper
Risk Assessment Review Committee (RARC) Reviewers
Health Effects Division (7509P)

TO: James Parker, RM51
Risk Management and Implementation Branch 1
Pesticide Re-Evaluation Division (PRD)

As part of Registration Review, the Pesticide Re-evaluation Division (PRD) of the Office of Pesticide Programs (OPP) has requested that the Health Effects Division (HED) evaluate the hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the currently registered uses of pesticides. This memorandum serves as HED's draft human health risk assessment of the dietary, occupational and residential exposures; and aggregate risk from the registered uses of d-phenothrin.

Table of Contents

1.0 Executive Summary

This draft risk assessment is in support of the registration review for d-phenothrin. This document addresses the exposures and risks associated with food, drinking water, occupational, and residential uses of d-phenothrin from existing uses.

d-Phenothrin, ([(3-phenoxyphenyl)methyl] 2,2-Dimethyl-3-(2-methyl-1-propenyl)cyclo propanecarboxylate), is a type I pyrethroid insecticide. Pyrethroids are synthetic esters derived from naturally occurring pyrethrins (insecticides derived from the extract of chrysanthemum flowers). Type I pyrethroids act on axons in the peripheral and central nervous system by interacting with sodium channels in mammals and/or insects. Technical grade d-phenothrin is composed of both cis and trans forms. d-Phenothrin and other pyrethroids are usually combined with synergists which enhance insecticidal activity by preventing enzymatic break down of the pyrethroid.

Use Profile

d-Phenothrin is used to control adult mosquitoes in outdoor residential and recreational areas. A tolerance of 0.01 parts per million is established for residues of the insecticide d-phenothrin in or on all food/feed crops following wide-area mosquito adulticide applications. It is also used for control of insects on ornamental plants; pets and their dwellings; and in outdoor and indoor areas of residential, recreational, commercial and industrial sites, and animal quarters. d-Phenothrin is formulated primarily as ready-to-use, pressurized liquid, powder, and emulsifiable concentrate formulations containing between 0.15% and 85.7% ai. It may be applied by ultra-low volume (ULV) ground (i.e., truck mounted fogger), air, and handheld ULV fogger equipment for vector mosquito adulticide control. It can also be applied by indoor foggers, automatic misting systems (e.g. animal quarters) and as pet spot-on and shampoos.

Phenothrin is also registered for use in an antimicrobial product (EPA Reg. Num. 397-13), which is co-formulated with three antimicrobial active ingredients (isopropyl alcohol, Alkyl Dimethyl Benzyl Ammonium Chloride [ADBAC], and Didecyl Dimethyl Ammonium Chloride [DDAC]) that is used to treat bacteria, fungi, virus, mold, mildew, and insects on carpets, surfaces of mattresses, sofa-upholstered chairs, non-upholstered chairs, bed springs, furniture and other non-porous, non-food contact surfaces in sites such as restrooms. This registered antimicrobial product label prohibits phenothrin use "*in food areas of food handling establishments, restaurants, or other areas where food is commercially prepared or processed*", as well as in serving areas while food is exposed or facility is in operation. There are currently no Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)-registered antimicrobial uses of phenothrin that could result in direct or indirect food contact, thus, antimicrobial uses are not expected to result in dietary exposure. This risk assessment focuses on the conventional uses of d-phenothrin, and not the antimicrobial uses.

Exposure Profile

Humans may be exposed to d-phenothrin from dietary, occupational, and residential exposures. Exposures through food and drinking water are expected based on the d-phenothrin mosquito control use applied over agricultural fields. Occupational and residential handler exposures are anticipated from the application of d-phenothrin. Residential post-application exposures are expected based on the use pattern of the chemical; however, occupational post-application exposures are not expected since re-entry activities are not likely based on the use pattern of d-phenothrin.

The toxicological profile of the majority of pyrethroids is characterized by rapid onset toxicity with associated acute, peak exposures. That is, pyrethroids tested in single and repeat dosing studies typically show that repeat exposures do not result in lower points of departure (PODs). For those pyrethroids, only a single day assessment is conducted. In contrast, d-phenothrin acute and repeat dose toxicity studies result in unique toxic effects and the doses at which these effects occur differ. Therefore, a single day assessment is not appropriate, and occupational and residential exposures from d-phenothrin are instead characterized as short-, intermediate-, or long-term, as appropriate for the exposure scenario.

All residential handler and post-application exposures are expected to be short-term, except for residential post-application exposure to pets treated with the spot-on product which is expected to be all durations (short-, intermediate-, and long-term). Occupational exposure to d-phenothrin is expected to be short- and intermediate-term in duration.

Hazard Identification
Pyrethroids have historically been classified into two groups, Type I and Type II, based on chemical structure and toxicological effects. d-Phenothrin is a Type I synthetic pyrethroid insecticide, which lacks an alpha-cyano moiety. Type I pyrethroid insecticides typically induce in rats a syndrome consisting of aggressive sparring, altered sensitivity to external stimuli, and fine tremor progressing to whole-body tremor and prostration (T-syndrome). Pyrethroids disrupt the voltage-gated sodium channels in the nervous system, resulting in neurotoxicity. d-Phenothrin did not induce the typical T-syndrome or neurotoxicity in rats, dogs or mice after acute, subchronic or chronic exposures. While d-phenothrin is part of the pyrethroid common mechanism group (CMG), it was not included in the October 2011 Pyrethrins/Pyrethroid Cumulative Risk Assessment document because it did not elicit a toxic response consistent with the common mechanism at the limit dose of 2000 mg/kg.

The effects on the liver are the most systemically sensitive endpoint following repeated oral exposure to d-phenothrin based on acceptable subchronic and chronic oral studies in rodents and dogs. These effects include increased liver weight, hepatocellular vacuolization and hypertrophy and, at higher doses, increased liver serum enzymes. Based on a 90-day inhalation study in rats, the primary inhalation exposure effects are histopathologic changes in the nasal turbinates. d-Phenothrin was not associated with any systemic toxicity up to the limit dose of 1000 mg/kg/day in a 3-week dermal toxicity study in rats. d-Phenothrin was not neurotoxic in rats following acute (2000 mg/kg) or subchronic exposure (20,000 ppm equivalent to 1456 mg/kg/day). d-Phenothrin was not toxic to rat fetuses. In a rat developmental study, minimal effects were observed at the highest dose tested. However, in a rabbit developmental study, significant maternal (increased abortions) and developmental toxicity (spina bifida and hydrocephalus) in fetuses were observed. In two acceptable rat reproduction studies, both systemic toxicity and reproductive/offspring toxicity occurred at the same doses with similar effects for offspring and dams in each study (organ weight changes and decreased body weight gain). Increased quantitative susceptibility, however, was seen in studies on pyrethroid pharmacokinetics (primarily conducted with deltamethrin) and increased quantitative juvenile susceptibility was observed in high dose guideline and literature studies with some pyrethroids (such as deltamethrin). d-Phenothrin is rapidly absorbed following oral administration to rats with nearly complete elimination in the urine and feces within 7 days. d-Phenothrin was classified by the HED Cancer Assessment Review Committee as "Not Likely to be Carcinogenic to Humans". Additionally, acceptable mutagenicity studies were negative for mutagenic potential.

Toxicological endpoints were selected for dietary, residential, and occupational exposure scenarios based on registered uses of d-phenothrin. Acute and chronic reference doses (RfDs) were selected for assessment of food and drinking water exposures. The acute RfD for females 13-49 was selected from a developmental toxicity study in rabbits. An acute RfD for the general population was not selected because no effect attributable to a single day oral exposure was observed in animal studies. A chronic RfD was selected from a 52-week feeding study in dogs. The toxicity endpoint for incidental oral exposures was selected from a 2-generation rat reproduction study. A toxicological endpoint from a 13-week inhalation study in rats was selected for assessment of the inhalation exposure pathway for workers and residential handlers/occupants. Toxicological endpoints for dermal exposure were not selected for this assessment based on dermal absorption studies for pyrethroids in general which indicate low dermal absorption (<5%) and a dermal toxicity study with d-phenothrin in which dermal effects were not observed at the limit dose.

HED considers the d-phenothrin toxicity database adequate to evaluate risk for individuals 6 years old and older. As of this publication, efforts to develop data in juvenile rats for the pyrethroid class are ongoing and remain a source of uncertainty in the evaluation of infant and young child exposure. Although the d-phenothrin toxicity profile lacks consistent evidence of neurotoxicity, it is a member of the pyrethroid class and was included in the pyrethroid common mechanism group. The underlying cause for the unique behavior of d-phenothrin is unclear at this time; therefore, the uncertainty in pharmacokinetics for infants and children identified for the pyrethroid group is also a concern for d-phenothrin. A Food Quality Protection Act (FQPA) Safety Factor (SF) of 3x for potential sensitivity was applied to the chronic dietary, incidental oral and residential inhalation assessments for children less than 6 years old. Despite the aforementioned uncertainty, HED is confident the selected PODs and the uncertainty factors provide sufficient protection for all age groups.

Dietary Exposure and Risk

HED conducted conservative unrefined acute and chronic dietary exposure assessments for d-phenothrin. These assessments included all commodities because of the all-crop tolerance. The assessments were based on the 0.01 ppm tolerance for all commodities, 100 percent crop treated assumptions, and conservative default processing factors. For drinking water, it incorporated the estimated water peak concentration of 0.0097 ppm, the solubility in water for acute and chronic dietary assessment. Results of the acute dietary assessment indicate that exposure and risk estimates for the population subgroup of concern, females 13-49 years, are not of concern. The acute dietary exposure estimate for females 13-49 years of age is <1.0% of the acute population adjusted dose (aPAD). Results of the chronic dietary assessment indicate that the general U.S. population and all other population subgroups have exposure and risk estimates that are not of concern. The chronic dietary exposure estimate for the highest exposed population subgroup, children 1-2 years of age, is 5.5% of the chronic population adjusted dose (cPAD). Based on d-phenothrin's cancer classification of "Not Likely", quantification of cancer risk is not required.

Residential Exposure and Risk
A screening-level approach was used for assessment of residential exposures by evaluation of the maximum application rate for all possible residential exposure scenarios of d-phenothrin. Residential handler and post-application exposures are expected to be short-term only, except for residential post-application exposures from pet spot-ons which are expected to be all durations.

No inhalation risks of concern were identified for any of the residential handler exposure scenarios assessed (an MOE ≥ 30 is not of concern). Estimated inhalation MOEs ranged from 410 to 2,200,000.

The majority of residential post-application risks estimated were not of concern (i.e., adult inhalation MOEs ≥ 30; children 1 to < 2 years old and children 3 to < 6 years old inhalation MOEs ≥ 100; and children 1 to <2 years old incidental oral MOEs ≥ 300). MOEs not of concern ranged from 340 to 240,000. However, residential post-application risks of concern were identified from inhalation exposures in animal quarters following treatment with an automated misting system (i.e., MOEs were 0.79 and 0.57 for adults and children 3 to < 6 years old, respectively).

Non-Occupational Spray Drift Exposure and Risk Assessment
A quantitative spray drift assessment was not conducted because d-phenothrin does not have a potential for spray drift exposures onto residential areas which are not already being assessed by the residential post-application assessment of exposures from turf following mosquito adulticide application.

Aggregate Exposure and Risk
For d-phenothrin, incidental oral and inhalation endpoints should not be aggregated because the toxicity endpoints for these exposure routes are not based on common specific target organ toxicity effects. Therefore, aggregate risks are represented by dietary and residential exposures alone. Acute and chronic aggregate risks of exposure to d-phenothrin are composed of exposure to residues in food and drinking water. Acute and chronic aggregate risks of <1.0% acute population adjusted dose (aPAD) and 5.5% chronic population adjusted dose (cPAD), respectively, are not of concern for the general U.S. population or any population subgroup. The recommended residential exposure for use in the children 1 to < 2 years old aggregate assessment for short- and intermediate-term exposures is from hand-to-mouth contact with carpet spot treated with a powder, which does not result in any risks of concern. This aggregate exposure scenario is protective for residential exposures of all durations, including long-term exposures to spot-on treated pets.

Occupational Exposure and Risk
The occupational inhalation handler exposure and risk estimates indicate that short- and intermediate-term inhalation MOEs are not of concern to HED (i.e., MOEs ≥ 30) with baseline attire. MOEs ranged from 630 to 3,500,000.

Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for d-phenothrin at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for d-phenothrin.

Dermal post-application exposure was not quantified due to the lack of dermal toxicity at the limit dose.

Environmental Justice
Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations.[1]"

Human Studies
This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from the Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1); the Agricultural Handler Exposure Task Force (AHETF) database; the Outdoor Residential Exposure Task Force (ORETF) database; and the 2012 Residential SOPs (Indoor Environments, Outdoor Fogging and Misting Systems, Treated Lawns/Turf, and Treated Pets); are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[2].

2.0 HED Conclusions and Recommendations

2.1 Data Deficiencies

There are no data deficiencies for d-phenothrin.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

No multiresidue monitoring protocol data were submitted by the registrant for d-phenothrin. No analytical method was recommended by the registrant for enforcement. However, FDA has tested d-phenothrin through their multiresidue protocols. d-Phenothrin is completely recovered through protocol 302, but only 60% remains after florisil cleanup, which is rarely used any more. Additionally, the FDA Pacific Regional Laboratory Northwest has developed a GC/MSD method

[1] http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf

[2] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

that recovers d-phenothrin. FDA uses this method for enforcement. No additional data are needed from the registrant (R. Loranger, 11/27/2007, D346331).

2.2.2 Tolerance Recommendations

The current tolerance expression is not in accordance with current guidance (S. Knizner, 5/27/2009) and needs revision. HED recommends that 40 CFR §180.647 be amended by revising the tolerance expression for residues of d-phenothrin in plant commodities. Tolerances are currently listed in 40 CFR §180.647 for residues of d-phenothrin at 0.01 ppm. The tolerance expression should be revised to: A tolerance of 0.01 parts per million is established for residues of the insecticide d-phenothrin in or on all food/feed crops following wide-area mosquito adulticide applications. **Compliance with the tolerance levels specified is to be determined by measuring only d-phenothrin in or on the commodity.**

2.2.3 Revisions to Petitioned-For Tolerances

Not Applicable.

2.2.4 International Harmonization

A tolerance of 0.01 parts per million is established for residues of d-phenothrin in or on all food/feed crops following wide-area mosquito adulticide applications. There are no Codex or Canadian maximum residue limits (MRLs) for d-phenothrin and harmonization is not an issue.

2.3 Label Recommendations

2.3.1 Recommendations from Residue Reviews

The d-phenothrin labels should have clear prohibitions against use in areas where food may be exposed i.e., "Do not use in commercial food-processing or preparation areas. In the home, all food-processing surfaces and utensils should be covered during treatment, or thoroughly washed before use. Cover exposed food." All labels should contain this prohibition.

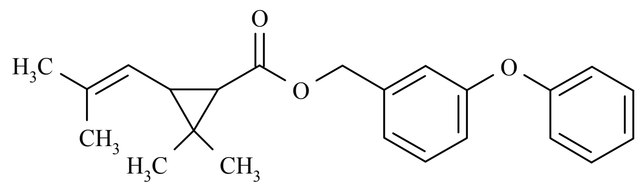
2.3.2 Recommendations from Occupational and Residential Assessment

d-Phenothrin product labels with automated misting system uses should be reviewed to ensure that related language clearly defines the proper usage of these systems. That is, whether the automated misting systems are intended to be used in an occupational or residential setting (or both). If d-phenothrin is intended to be used in automated misting systems in occupational settings only, the label should explicitly state this and identify specific occupational use sites (e.g., animal quarters). Further, the label should clearly state whether the systems are for indoor or outdoor usage (or both), since this could have an impact on potential human health exposures. For example, the product label EPA Reg. No. 1021-2576 states, "Not for use in outdoor residential misting systems (indoor and outdoor)." However, while the label clearly states that the product is intended for use in animal quarters, it does not make clear whether this includes residential or commercial animal quarters, or both.

3.0 Introduction

3.1 Chemical Identity

The nomenclature of d-phenothrin is provided in Table 3.1.

TABLE 3.1 d-Phenothrin Nomenclature.	
Chemical Structure	
Common Name	d-Phenothrin; Phenothrin; Sumithrin
Empirical Formula	C23H26O3
IUPAC Name	3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate or 3-phenoxybenzyl (1*RS*)-*cis-trans*-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate or 3-phenoxybenzyl (±)-*cis-trans*-chrysanthemate
CAS Name	(3-phenoxyphenyl)methyl 2,2-dimethyl-3-(2-methyl-1-propenyl) cyclopropanecarboxylate
CAS Registry Number	026022-80-2
Chemical Class	Type 1 Pyrethroid

3.2 Physical/Chemical Characteristics

A detailed description of the physicochemical properties of d-phenothrin is provided in Appendix B. The reported solubility of d-phenothrin is very low (<9.7 µg/L at 25°C). It has a low vapor pressure (1.43×10^{-7} mm Hg @ 21°C), and a calculated Henry's Law Constant of 6.80×10^{-6} atm-m^3/mol. Based on these properties, and its tendency to bind to soils, organic matter, particulate and sediments, the compound is not expected to volatilize substantially. The octanol/water partition coefficient for d-phenothrin is 1.03×10^{6}, which suggests a potential for bioaccumulation.

3.3 Pesticide Use Pattern

d-Phenothrin is currently registered for use as a wide-area mosquito adulticide for application over agricultural areas. d-Phenothrin currently has no registered uses on food (other than the mosquito control use), and d-phenothrin labels should have clear prohibitions against use in areas where food may be exposed i.e., "Do not use in commercial food-processing or preparation areas. In the home, all food-processing surfaces and utensils should be covered during treatment, or thoroughly washed before use. Cover exposed food."

In addition to the mosquito adulticide use, d-phenothrin is also used for control of insects on ornamental plants; pets and their dwellings; and in outdoor and indoor areas of residential, recreational, commercial and industrial sites, and quarters. d-Phenothrin is formulated primarily as ready-to-use, pressurized liquid, powder, and emulsifiable concentrate formulations containing between 0.15% and 85.7% ai. It may be applied by ultra-low volume (ULV) ground (i.e., truck mounted fogger), air, and handheld ULV fogger equipment for vector mosquito adulticide control. It can also be applied by indoor foggers, automatic misting systems (i.e., quarters including colt, donkey, horse and pony barns, goat and sheep pens, corrals, paddocks, stables, horse trailers, kennels, animal research facilities, show animal and race horse quarters, livestock loafing areas, sheds, and zoos) and as pet spot-on and shampoos.

Table 3.3.1 Summary of Directions for Use for d-Phenothrin

Application Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Application Rate	Use Directions and Limitations
Liquid Formulation for Use with Backpack and Handheld Sprayers in Outdoor Residential, Commercial, Recreational Areas and In and Around Horse Barns	MGK®2965 (10%) EPA Reg. No. 1021-2573 0.74 lb d-phenothrin/gallon	1 fl oz of concentrate/gallon spray solution or **0.006 lbs ai/gallon of solution**	**For Outdoor Surface Applications:** · Do not apply by air or with hand held or truck mounted cold aerosol ULV fogging devices. · Direct applications into tall grass and shrubbery, around lawns and other areas or surfaces where pests may harbor or rest. **For Indoor Horse Barn Use:** · Do not exceed maximum application rate of 0.25 lb ai/1000 sq ft or 38 fl oz. of MGK 2965 product per 1,000 sq ft. Do not apply more than 1 time per day.
Outdoor Residential Misting Systems		Maximum total daily application per nozzle = **$6.4x10^{-8}$ lb ai/ft^3** (estimated using the 2012 Residential SOPs and assuming an 8 ft nozzle height)	· No more than 185 seconds of total daily application for 0.023% solution (16 fl oz/ 55 gallons water); · No more than 93 seconds of total daily application for 0.046% solution (32 fl oz/ 55 gallons water); · No more than 85 seconds of total daily application for 0.051% solution (35 fl oz/ 55 gallons water). Not registered for use in automatic ULV spraying systems in the State of New York.
Automatic Misting System, Backpack and Handheld Sprayer, ULV Fogging Equipment Only for use in barns (horse, pony, colt, mule, donkey); pens	MGK 2935 (10% ai) EPA Reg. No. 1021-2576 0.8758 lb d-phenothrin/gallon	*Automatic Misting System:* Mix: 0.5 gal concentrate/55 gal of water = **0.48 lb ai/ 55 gallons** 4.8 fl.oz/1000 ft^3/day (**0.000031 lb ai/ft^3**) *Adult Mosquito and Fly Control Outdoors:* Applied	· Do not enter or allow others to enter treated area until sprays have dried. · Not for use in outdoor residential misting systems (indoor and outdoor). · Do not use in barns that are occupied by domestic animals (poultry, cattle, horses, swine,

Table 3.3.1 Summary of Directions for Use for d-Phenothrin			
Application Timing, Type, and Equip.	**Formulation [EPA Reg. No.]**	**Application Rate**	**Use Directions and Limitations**
(goat, sheep); shelters corrals; paddocks holding pens; stables; horse trailers; kennels; animal research facilities; show animal quarters; race horse quarters; livestock; loafing areas and sheds; and Zoos.		with cold aerosol, ultra-low volume (ULV) sprayers, hand-held sprayer, mechanical, or compressed air spraying or fogging equipment. Dilution : 0.013 lb ai/ 1.5 gal H_2O = **0.0091 lb ai/gal soln** As Surface Spray: 1 gal soln to 4,562 ft^2 = **2.0×10^{-6} lb ai/ft^2** To treat shrubbery and vegetation where mosquitoes may rest: 1 gal soln/2.5 acres = **0.0036 lb ai/A**	goats, and sheep) that may be used for human consumption · This product is not recommended for use in thermal generating equipment.
Ground /Aerial Equipment (EC) and Handheld ULV Fogger for Mosquito Adulticide Application	Multicide Fogging Concentrate 2807 (10% ai) EPA Reg. No. 1021-1807 0.847 lb d-phenothrin/gallon Multicide Mosquito Adulticiding Concentrate 2705 (10% ai) EPA Reg No 1021-1688 0.74 d-phenothrin/gallon	Use 0.62 fl. oz. of the undiluted spray per acre (**0.0036 lb ai/acre** or **8.3×10^{-8} lb ai/ft^2**). Human flagging is prohibited. Flagging to support aerial applications is limited to use of the Global Positioning System (GPS) or mechanical flaggers.	· **For use only by certified applicators.** · Do not treat a site with more than 0.0036 pounds of Sumithrin® per acre in a twenty-four hour [24-hr] period. · Do not exceed 0.1 pounds of d-phenothrin per acre in any site in one year. · Not for use in outdoor residential misting system. · Do NOT use portable backpack equipment for application in enclosed spaces.
Indoor Household Sprays – Space Spray (aerosol can) Indoor Household Sprays – Surface/Crack and Crevice Spray (aerosol can)	Deadpest (2%) EPA Reg. No.: 65987-3	**0.020 lb ai/14 oz can** (2.3×10^{-5} lb ai/m^3) Deposited Residue: 2.56 µg/cm^2	· Spray 10 grams (10 seconds) per 1,000 cubic feet of space. Keep treated areas closed for at least 30 minutes after spraying. · Wait two (2) hours after application, and then open windows, vents and doors for two (2) hours. · Only protected handlers may be in the area during application. · Do not enter or allow others to enter the treated area until sprays have dried.
Indoor Aerosol Spray for Bedbugs	Multicide Lice and Dust Mite Spray 27911 (0.40%)	**0.0040 lb ai/ 17 oz can**	· For bed bug treatment, apply as a spot treatment to cracks and crevices. Apply as a surface spray to carpet, mattresses, box springs,

Table 3.3.1 Summary of Directions for Use for d-Phenothrin			
Application Timing, Type, and Equip.	**Formulation [EPA Reg. No.]**	**Application Rate**	**Use Directions and Limitations**
			walls, furniture, bedding, floor and floor coverings. · Then clean and air out mattresses and box springs.
Flea and Ticks Spray for Carpets and Furniture (aerosol can)	NYLAR® Pressurized Spray 2618 (0.30%) EPA Reg. No.: 1021-1622	**0.0030 lb ai/16 oz can**	· Surface directed spray. Spray uniformly using a sweeping motion to carpets, rugs, drapes and all surfaces of upholstered furniture. · One treatment with this spray gives continuous flea protection for 210 days.
Outdoor House and Garden Sprays (aerosol can)	Multicide® House and Garden Insect Killer 2553 (0.2%) EPA Reg. No. 1021-1588	**0.0020 lb ai/16 oz can** *Outdoors:* Spray areas at a rate of 1–3 seconds per cubic yard. Directly on insects on ornamentals: Spray rows at a rate of 1 foot per second. *Indoors:* As Space Spray: 5-10 seconds for average room (keep room closed for 15 minutes after spraying). *Surface directed (Spot) Spray:* 2 seconds per linear foot. *Carpet treatment:* 1 sq ft/sec	· Do not use in food areas of food handling establishments, restaurants, or other areas where food is commercially prepared or processed. · Do not allow people or pets to enter treated areas until vapors, mists, and aerosols have dispersed, and the treated area has been thoroughly ventilated. · Wait two (2) hours after application. · All outdoor applications must be limited to spot or crack-and-crevice treatments only, except for treatment to soil or vegetation around structures and applications to lawns, turf, and other vegetation.
Indoor Household Carpet Powder RTU 16 oz container (powder directly applied to carpets)	Hartz Reference #150 (0.495%) EPA Reg. No. 2596-132	**0.0050 lb ai/ can**	· Only spots less than 3 feet by 3 feet per room may be applied with this product. · Leave on for two hours, then thoroughly vacuum to remove all insecticidal product. · Do not reapply this product within 30 days.
Total Release Fogger (Ready-to-Use Formulation for Indoor Environment)	Bengal Indoor Dri-Fogger II (2%) EPA Reg. No. 68543-2	**$7.8x10^{-7}$ lb ai/ft^3** One 3 oz. canister of fogger will treat a room up to 24 ft x 25 ft with an 8 foot ceiling. One 5 oz. canister of fogger will treat a room up to 25 ft x 40 ft with an 8 foot ceiling.	· Do not enter or allow others to enter the treated area until the sprays have dried. · Wait two (2) hours after application, then open windows, vents and doors for two hours. · DO NOT use more than one fogger per room. · Do not use in a room 5 ft. X 5 ft. or smaller; instead, allow fog to enter from other rooms.

Table 3.3.1 Summary of Directions for Use for d-Phenothrin

Application Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Application Rate	Use Directions and Limitations
Handheld ULV Fogger (Liquid Concentrate) (Outdoor Residential Use Only)	Multicide 29131; Multicide 29132; Multicide 29133 (0.15%) EPA Reg. Nos.: 1021-1863; 1021-1865; 1021-1866	1.5 fl oz/1000 sq ft (**0.00503 lb ai/A**) Fog at the rate of 1.5 fluid ounces per 1000 sq ft (a 25' x40' area). Apply one pump of the fogger trigger every 3 to 4 seconds to obtain the best fog quality. It will take approximately 30 pumps of the fogger trigger to fog 1000 sq ft. 1 qt of product will be required to treat ½ acre.	· Do not use indoors or in enclosed spaces · Not for use in outdoor residential misting systems. · Do not remain in treated area. Exit area immediately and remain outside the treated area until aerosols, vapors and/or mists have dispersed · Do not apply more than 1 time per day. · Fog in late afternoon or early dusk when wind is calm and insect activity is increasing. Do not treat if wind is greater than 5 mph, because the fog will dissipate too quickly.
Direct Application to Pets (Shampoo for Dogs)	Hartz Ref. 133 (0.27%) EPA Reg. No.: 2596-162 (18 oz/532 ml bottle)	**8.9×10^{-5} lb ai/pet** Use 1 tablespoon (15 mls) of shampoo per 15 lb of body weight	· Do not apply as a broad carpet treatment. · Do not reapply this product within 30 days. · Do not apply this product to puppies less than 6 months of age. · Do not apply this product to cats or kittens.
Direct Application to Pets (Spot-on for Dogs)	Hartz® Reference #124 (85.7%) EPA Reg. No: 2596-156	4 to 15 lbs: 0.04 fl oz 16 to 30 lbs: 0.06 fl oz 31 to 60 lbs: 0.14 fl oz > 60 lbs: 0.21 fl oz	· Do NOT use on cats. · Keep cats away from treated dogs for 24 hours. · Do not use on dogs or puppies weighing under 5 lbs. · Put between animal blades.

3.4 Anticipated Exposure Pathways

Humans may be exposed to d-phenothrin from dietary, occupational, and residential exposures. Exposures through food and drinking water are expected based on the d-phenothrin mosquito control use applied over agricultural fields. Occupational and residential handler exposures are anticipated from the application of d-phenothrin. Residential post-application exposures are expected based on the use pattern of the chemical; however, occupational post-application exposures are not expected since re-entry activities are not likely based on the use pattern of d-phenothrin. d-Phenothrin does not have a potential for spray drift exposures onto residential areas which are not already being assessed by the residential post-application assessment of exposures from turf following mosquito adulticide application.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.archives.gov/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and/or the CDC under the National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA), and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

4.1 Toxicology Studies Available for Analysis

The d-phenothrin toxicity database is adequate to evaluate risk for children > 6 years old and adults. However, there are on-going efforts to develop data to inform the potential sensitivity of infants and children younger than 6 years of age to pyrethroids as a class, which is discussed further in Section 4.4.1. Despite these scientific efforts, HED is confident that it has chosen points of departure and uncertainty factors in this risk assessment which are health protective and have a strong scientific foundation.

The data from the following guideline studies in experimental animals were used to evaluate the hazard potential of d-phenothrin:

- 21-Day Dermal Study in the Rat
- 28-Day Inhalation Toxicity in the Rat
- 90-Day Oral Studies in the Rat and Dog
- Chronic/Carcinogenicity Studies in the Rat, Mouse, and Dog
- Developmental Studies in the Rat and Rabbit
- Reproduction Studies in the Rat
- Acute Neurotoxicity Study (ACN), Subchronic Neurotoxicity Study (SCN), in the Rat[3]
- Immunotoxicity Study in the Rat
- Mutagenicity Battery of Studies
- Metabolism Study (rat)

In addition, numerous studies from the scientific literature conducted over several decades describe the pharmacodynamic and pharmacokinetic profile of pyrethroids; this scientific literature has been recently reviewed by several groups (Soderlund *et al*. 2002; Shafer *et al*., 2005; Wolansky and Harrill 2008). d-Phenothrin was not included in the Wolansky and WIL studies. It was excluded from the full WIL Laboratory special acute study (Herberth 2010) because it did not elicit neurotoxic effects up to the maximum tested dose, 5000 mk/kg, in the range finding study. The exclusion of d-phenothrin from this study further discriminates it from other pyrethroids.

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

^{14}C-d-Phenothrin (cis- or trans-isomer) administered to rats at a single low dose (4 mg/kg), single high dose (200 mg/kg), and following 14-days repeated administration at 4 mg/kg had about 96-100% of C^{14} excreted in urine and feces in about 7 days. More than 90 percent of the excreted radioactivity for both sexes and for both the *cis*- and *trans*-isomer was collected within the first two (2) days for each dose group (low, high, repeated). Residues in tissues at 7 days were quite low, with fat having the highest levels. Most urinary metabolites were cleaved esters (major metabolite was 4'-OH-PB acid sulfate). Most fecal metabolites were esters (i.e., not cleaved). Metabolites were conjugated with glucuronide, sulfuric acid or glycine. No sex differences were noted.

4.2.1 Dermal Absorption

There are no dermal absorption studies available with d-phenothrin. A conservative dermal absorption estimate of 2.0% was selected in the 2008 risk assessment (D342813) based on available dermal absorption studies in pyrethrins and/or pyrethroids. In a cypermethrin dermal metabolism study, absorption ranged from 0.3-1.8% (MRID 43261603). A dermal absorption study (2004) of pyrethrins in humans indicated 0.22% dermal absorption (MRID 46382501,

[3] A 10x database uncertainty factor used in the previous risk assessment for the absence of acceptable neurotoxicity studies (R. Daiss, 7/2/2008) has been removed because this requirement has been fulfilled.

TXR 0052902). In the 2004 study with pyrethrins, the exposure period was 8 hours in four male volunteers. Subjects were monitored for 120 hours. Dermal penetration of 0.22% was calculated as the sum of urinary and fecal excretion.

Based on a 2% dermal absorption factor, there was no concern from developmental effects seen in the rabbit developmental study with a NOAEL of 30 mg/kg/day for spina bifida resulting in a dermal equivalent of 1500 mg/kg/day, which exceeded the limit dose of 1000 mg/kg/day. However, the pyrethroid cumulative risk assessment utilized a conservative 5% dermal absorption factor for all the pyrethroids. Assuming 5% dermal absorption results in a dermal equivalent dose of 600 mg/kg/day using the NOAEL of 30 mg/kg/day from the rabbit developmental study and 2000 mg/kg/day (2x above the limit dose) using the LOAEL of 100 mg/kg/day. The 5% dermal absorption factor is very conservative and it is likely much less for d-phenothrin. Therefore, dermal exposure assessments have not been performed in this assessment.

4.3 Toxicological Effects

d-Phenothrin was not included in the October 2011 Pyrethrins/Pyrethroid Cumulative Risk Assessment document because it did not elicit a toxic response consistent with the pyrethroid common mechanism at the limit dose of 2000 mg/kg (D394576, K. Whitby 2011). d-Phenothrin differs from other pyrethroid insecticides in that it does not produce the typical neurotoxic effects (tremors) following oral gavage of high doses. The only clinical sign of toxicity observed following a single oral dose of 5000 mg/kg was the secretion of an oily substance by both sexes of rats on Day 1. d-Phenothrin did not elicit neurotoxicity in rats at the limit dose (2000 mg/kg) in an acute neurotoxicity study. Similarly d-phenothrin was not neurotoxic in rats in a subchronic neurotoxicity study following dietary administration of 20,000 ppm (equivalent to 1456 mg/kg/day) for 90 days. d-Phenothrin did not result in any systemic toxicity following dermal exposure for 21 days up to the limit dose (1000 mg/kg/day). The lack of toxicity from dermal exposures is related to the poor penetration of d-phenothrin through the skin. Typically, pyrethroids have a low dermal absorption value of < 5% and a high rate of metabolism. Pyrethroids, including d-phenothrin, are lipophilic, and much of the radioactivity measured in the skin of dermal penetration studies with pyrethroids is captured in the upper dermal layers and not available for absorption or systemic circulation.

The liver is the target organ of toxicity following repeated oral exposure to d-phenothrin. These effects include increased liver weight, hepatocellular vacuolization and hypertrophy, and, at higher doses, increased liver serum enzymes. The most sensitive effects from repeated inhalation exposure are portal of entry effects (histopathological changes in the nasal turbinates in both sexes). The inhalation study also indicated histological effects on the liver, thyroid and adrenal, which are of borderline toxicological significance alone, but which are supported in part by the increased organ weights and histological findings of similar occurrence in some oral studies.

No increased pre- or post-natal susceptibility was observed following a developmental toxicity study in the rat or a 2-generation reproductive toxicity study. In the developmental rat study, effects were seen at a high dose (3000 mg/kg/day) and consisted of decreased weight gain and decreased food consumption (maternal) and decreased fetal weight and developmental delay (small and immature fetuses). d-Phenothrin demonstrated qualitative and quantitative susceptibility in one rabbit developmental study based on an observation of spina bifida in one fetus at doses lower than those at which maternal effects were seen. Significant maternal (increased abortions) and developmental toxicity (spina bifida and hydrocephalus) in fetuses were observed in this rabbit developmental study. The spina bifida effect in rabbits was considered significant as it is an indicator of neurotoxic effects and because the use of methylcellulose as a vehicle may have resulted in an underestimation of toxicity (Crofton et al 1995). Indications of neurotoxicity from this rabbit developmental study included presence of spina bifida at the mid-dose of 100 mg/kg/day, microphthalmia at 300 mg/kg/day and hydrocephaly at the high-dose of 500 mg/kg/day. While these neurodevelopmental effects were seen in only a single fetus each, the observations of spina bifida and microphthalmia were considered significant because they are uncommon in untreated rabbits yet they occurred together in the d-phenothrin rabbit developmental study. In a second developmental study using the same strain of rabbit (New Zealand White) conducted at a higher dose (750 mg/kg/day using the same vehicle, aqueous methyl cellulose) and in a larger number of rabbits (60 rabbits per dose vs 20, and treated for a longer time from GD 6-28 inclusive vs GD 7-19 in the first study), no developmental effects including hydrocephalus were seen. The Agency reviewed the findings in this study and concluded that the high mortality of does and the significantly increased resorptions seen in this study may have masked the detection of developmental toxicity including the spina bifida seen in the first study.

d-Phenothrin produced adrenal cortex vacuolation in the 1-year dog feeding study and 90-day inhalation toxicity study in rats. Additionally, the 90-day inhalation toxicity study also resulted in follicular thyroid cell enlargement. Hepatocellular enlargement was also produced in the 1-year dog feeding study and the 90-day inhalation study, but was not always associated with thyroid toxicity in these studies at the doses tested. d-Phenothrin exhibited no potential to cause adverse estrogenic or (anti-)androgenic effects even at a limit dose of 1000 mg/kg per day (Yamada et al. 2003). When tested in the Ishikawa Var-I human endometrial cancer cell line and the T47D human breast cancer cell line, d-phenothrin demonstrated significant estrogenicity at concentrations of 10 μM. d-Phenothrin did not show statistically significant estrogen antagonist activity or acted as progestin in this assay (Garey and Wolff. 1998). The endpoints selected for chronic dietary, incidental oral and inhalation exposure are protective of any potential endocrine effects. d-Phenothrin was not included in the EDSP list of 52 chemicals (Tier 1, List 1 or Tier 1, List 2).

d-Phenothrin has been classified by the CARC as “Not Likely to be Carcinogenic to Humans” based on EPA’s 2005 Guidelines for Carcinogen Risk Assessment (TXR 0054233). Rat liver tumors, namely hepatocellular carcinomas, occurred only at excessively toxic doses (limit dose), and mouse liver hepatocellular adenomas, which are common, did not achieve statistical significance ($p<0.01$). Additionally, an acceptable battery of mutagenicity studies were negative for mutagenic potential.

D-phenothrin has a low acute toxicity by oral (category IV), dermal (category III), and inhalation (category IV) routes of exposure. It is a mild eye irritant (Category III) but is not a skin irritant (category IV) or a skin sensitizer.

The toxicity profile for d-phenothrin is provided in Appendix A.

4.4 Food Quality Protection Act Safety Factor for Infants and Children[4]

There were no indications of fetal toxicity or post/pre-natal susceptibility in the rat developmental study and in the 2-generation reproduction studies in rats. Phenothrin demonstrated qualitative and quantitative susceptibility in one rabbit developmental study based on an observation of spina bifida in one fetus at doses lower than those at which maternal effects were seen. Since spina bifida could be a single dose effect during the development of the fetus, this endpoint was relied on for assessing acute dietary risk for only women of child bearing age (not children less than 6). Furthermore, a clear NOAEL was identified for both the pregnant rat and the fetus, therefore the FQPA safety factor is reduced from 10x to 1x.

Studies from the scientific literature point to enhanced quantitative susceptibility in juveniles related to pyrethroid pharmacokinetics (see section 4.3 and 4.4.3). Consequently, the Agency is retaining an FQPA SF of 3x for assessing risk to children less than 6 years old. The Agency is confident that the available studies in the toxicity database and scientific literature adequately characterize risk to children 6 years and older and to adults; therefore, the 3x FQPA SF does not apply to these age groups,

4.4.1 Completeness of the Toxicology Database

The toxicology database for d-phenothrin is complete including developmental toxicity studies in rats and rabbits, a reproduction study in rats, and acute neurotoxicity (ACN) and subchronic neurotoxicity (SCN) studies. At this time, the Agency lacks additional data to address the potential for juvenile sensitivity to many pyrethroids, including d-phenothrin.

The Agency is expecting additional *in vitro* and *in vivo* data. In 2010, the Agency requested proposals for study protocols that could identify and quantify potential juvenile sensitivity and received a single response from the Pyrethrin and Pyrethroids Technical Working Group (PPTWG), a conglomerate of pyrethroid registrants. The PPTWG protocol was reviewed during a July 2010 FIFRA SAP meeting. Based on comments from the SAP, the initial study proposal was refined. At the present time, the CAPHRA is 1) conducting *in vitro* studies demonstrating the interaction of pyrethroids with exogenously expressed rat and human VGSCs in *Xenopus* oocytes; 2) conducting *in vitro* studies demonstrating interaction of pyrethroids with VGSCs in rat neurolemma cells; 3) developing rat and human PBPK models, including additional pharmacokinetic data; and 4) conducting *in vivo* behavioral testing using auditory startle testing in rats. As more data for individual pyrethroids become available, the Agency will determine whether re-evaluation of the age-related sensitivity of pyrethroids is appropriate.

The uncertainty regarding the protectiveness of the intraspecies uncertainty factor raised by the literature studies and the absence of the requested data warranted the application of a 3X FQPA SF for risk assessment for infants and children <6 years of age (See section 4.4.3).

[4] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

4.4.2 Evidence of Neurotoxicity

d-Phenothrin differs from other pyrethroid insecticides in that it does not produce the typical neurotoxic effects (tremors) following oral gavage of high doses. The only clinical sign of toxicity observed following a single oral dose of 5000 mg/kg was the secretion of an oily substance by both sexes of rats on Day 1. d-Phenothrin did not elicit neurotoxicity in rats at the limit dose (2000 mg/kg) in an acute neurotoxicity study. Similarly, d-phenothrin was not neurotoxic in rats in a subchronic study following dietary administration of 20,000 ppm (1456 mg/kg/day) for 90 days. The only indication of neurotoxicity was seen in a rabbit developmental study with spina bifida in fetuses.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

No increased pre- or post-natal susceptibility was observed in the rat developmental and 2-generation reproduction studies. In rabbits, there was fetal susceptibility in one study, but not in another study conducted at a much higher dose (which also resulted in high mortality). d-Phenothrin was not neurotoxic in the ACN or SCN studies conducted at high doses in rats. There is no developmental neurotoxicity (DNT) study for d-phenothrin. The Agency has reviewed existing pyrethroid data and concluded that the DNT is not a particularly sensitive study for comparing the sensitivity of young and adult animals to pyrethroids (USEPA 2010, TXR 0055306). Additionally, the degree of concern for these effects in fetuses is low because the effects seen in the developmental rabbit study have clearly defined NOAEL/LOAELs and the POD selected for risk assessment is protective of these effects.

High-dose studies in the scientific literature indicate that younger animals are more susceptible to the toxicity of pyrethroids. For example, Sheets *et al* (1994) found increased brain deltamethrin levels in young rats (PND 11 and 21) relative to adult rats (PND 72). These age-related differences in toxicity are principally due to age-dependent pharmacokinetics. The activity of enzymes associated with the metabolism of pyrethroids increase with age (Anand *et al*, 2006). However, in context, normal dietary or residential exposures of juveniles are not expected to overwhelm their ability to metabolize pyrethroids. In support, at a dose of 4.0 mg/kg deltamethrin (near the Wolansky study LOAEL value of 3.0 mg/kg for deltamethrin), the change in the acoustic startle response was similar between adult and young rats (Sheets *et al*, 1994). In addition, EPA's Office of Research and Development (ORD) recently developed an age-dependent PBPK model for deltamethrin (Tornero-Velez *et al,* 2010) that predicts a 3–fold increase of pyrethroid in neuronal tissue in younger animals compared to adults. There are several studies (*in vitro* and *in vivo*) that indicate that PD contributions to pyrethroid toxicity are not age-dependent. Examination of specific VGSCs has demonstrated that there is a lack of increased sensitivity in either juvenile specific isoforms (Meacham *et al*, 2008) or in human isoforms compared to rat variants (Tan and Soderlund, 2009).

After reviewing the extensive body of peer-reviewed literature on pyrethroids, the Agency has no residual uncertainties regarding age-related sensitivity for women of child bearing age as well as for all adult populations and children >6 years of age, based on the absence of pre-natal sensitivity observed in 76 guideline studies for 24 pyrethroids and the scientific literature. Additionally, no evidence of increased quantitative or qualitative susceptibility was seen in the pyrethroid scientific literature related to pharmacodynamics. The Agency is retaining a 3X uncertainty factor to protect for exposures of children <6 years of age based on the increased quantitative susceptibility seen in studies on pyrethroid PK and the increased quantitative juvenile susceptibility observed in high doses studies, such as the deltamethrin guideline DNT and 2-generation reproduction studies.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties with regard to dietary or residential exposure. The dietary exposure assessments are based on conservative residue levels that account for parent and metabolites of concern, processing factors, and percent crop treated assumptions. Furthermore, conservative, upper-bound assumptions were used to determine exposure through drinking water and residential sources, such that these exposures have not been underestimated. The residential exposure assessment incorporates conservative assumptions in the assessment of adults and children; the exposure estimates in this analysis are unlikely to underestimate actual exposure.

4.5 Toxicity Endpoint and Point of Departure Selections

4.5.1 Dose-Response Assessment

Toxicity endpoints and points of departure (PODs) for dietary (food and water), occupational, and residential exposure scenarios are summarized below. A detailed description of the studies used as a basis for the selected endpoints are presented in Appendix A.

An acute dietary endpoint for the general population was not selected because no effect attributable to a single (or few) day(s) oral exposure was observed in animal studies. An acute POD of 30 mg/kg/day for females 13-49 years of age was selected from a rabbit developmental study based on fetal effects (spina bifida) at 100 mg/kg/day. The total UF is 100 (an interspecies scaling factor of 10X, an intraspecies variability factor of 10X, an FQPA SF of 1X).

A chronic dietary endpoint of 7.1 mg/kg/day (NOAEL) was selected from a chronic toxicity study in dogs based on hepatocellular enlargement in the liver and focal degeneration in the adrenal cortex in both sexes. The total UF for the general population, including children >6 years old, is 100 (an interspecies scaling factor of 10X, an intraspecies variability factor of 10X, an FQPA SF of 1X). However, the total UF for children <6 years old is 300 (an interspecies scaling factor of 10X, an intraspecies variability factor of 10X, an FQPA SF of 3X to account for the juvenile susceptibility).

For incidental oral exposures (all durations), a POD of 50 mg/kg/day was selected from a 2-generation rat reproduction study with a LOAEL of 150 mg/kg/day based on: decreased body weight (4-6%) and increased liver weight in F_0 and F_1 parental animals; an increase in absolute and relative spleen weight, and decreased absolute uterine weight in F_1 adults; decreased body weight gain during lactation of F_{2b} pups; decreased litter size of F_{1b} litters; decreased absolute heart and kidney weight in F_{2b} males; and increased relative liver weight in male and female F_{2b} pups. For children <6 years old, the level of concern (LOC) for MOE is 300 (an interspecies scaling factor of 10X, an intraspecies variability factor of 10X, an FQPA SF of 3X to account for the juvenile susceptibility).

Dermal risk exposures were not assessed in the 2008 risk assessment based on the lack of dermal toxicity of d-phenothrin in rats in a 21/28 day study tested at the limit dose of 1000 mg/kg/day and the use of a dermal absorption factor of 2%. Based on this, there was no concern from developmental effects seen in the rabbit developmental study with a NOAEL of 30 mg/kg/day for spina bifida resulting in a dermal equivalent of 1500 mg/kg/day which exceeded the limit dose of 1000 mg/kg/day. However for this assessment, based on the cumulative risk assessment of pyrethroids, a 5% dermal absorption factor is proposed which will result in a dermal equivalent of 600 mg/kg/day using the NOAEL of 30 mg/kg/day from the rabbit developmental study. The 5% dermal absorption factor is very conservative and it is likely much less for d-phenothrin. Therefore, dermal exposures assessments are not needed.

For short-term and intermediate-term inhalation exposures, a POD of 0.104 mg/L was derived from a 90-day inhalation study in rats based on histopathological changes in the nasal turbinates at the LOAEL of 0.291 mg/L. For the calculation of the human equivalent concentration/human equivalent dose (HEC/HED) see Table 4.5.4.3 and Appendix D. The residential LOCs are 30 (an interspecies scaling factor of 3X, an intraspecies variability factor of 10X, an FQPA SF of 1X) for all populations, except children <6 years old for which the LOC is 100 (an interspecies scaling factor of 3X, an intraspecies variability factor of 10X, an FQPA SF of 3X). The occupational LOC is 30 (an interspecies scaling factor of 3X and an intraspecies variability factor of 10X).

4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

Based on the effects seen for the different routes of exposure, it is not recommended to combine any of the routes.

4.5.3 Cancer Classification and Risk Assessment Recommendation

d-Phenothrin has been classified by the HED Cancer Assessment Review Committee as "not likely to be carcinogenic to humans" (TXR No. 0054233). Rat liver tumors occurred only at excessively toxic doses (limit dose), and mouse hepatocellular adenomas, which are common, did not achieve statistical significance ($p<0.01$). Additionally, acceptable mutagenicity studies were negative for mutagenic potential. Quantification of cancer risk is not required.

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Toxicological doses/endpoints selected for the d-phenothrin risk assessment are provided in Tables 4.5.4.1 and 4.5.4.2. Human equivalent concentration/human equivalent dose (HEC/HED) are provided in Table 4.5.4.3 and Appendix D.

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for d-Phenothrin for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, including Infants and Children)	An acute RfD for the general population or any population subgroups was not selected because no effect attributable to a single (or few) day(s) oral exposure was observed in animal studies.			
Acute Dietary (Females 13-49 years of age)	NOAEL = 30 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Acute RfD = 0.3 mg/kg/day aPAD = 0.3 mg/kg/day	Developmental Toxicity Study – rabbit MRID 41230003 Developmental LOAEL = 100 mg/kg/day based on spina bifida.
Chronic Dietary (All Populations except children <6 years old)	NOAEL= 7.1 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF= 1x	Chronic RfD = 0.07 mg/kg/day cPAD = 0.07 mg/kg/day	Chronic Toxicity study in dogs MRID 40276401 Chronic toxicity LOAEL = 26.8 mg/kg/day based on hepatocellular enlargement in the liver and focal degeneration in the adrenal cortex in both sexes.
Chronic Dietary (children <6 years old)	NOAEL= 7.1 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF= 3x	Chronic RfD = 0.07 mg/kg/day cPAD = 0.02 mg/kg/day	Chronic Toxicity study in dogs MRID 40276401 Chronic toxicity LOAEL = 26.8 mg/kg/day based on hepatocellular enlargement in the liver and focal degeneration in the adrenal cortex in both sexes.
Incidental Oral Short-Term (1-30 days), Intermediate-Term (1-6 months), and Long-Term (> 6 months) (children <6 years old)	NOAEL= 50 mg/kg/day	UF_A= 10 x UF_H= 10 x FQPA SF= 3x for Children <6 years	Residential LOC for MOE = 300 for Children <6 years	2-generation rat reproduction study MRID 40276404 & 44082201 LOAEL = 150 mg/kg/day based on decreased F1 and F2 pup weights (6-12%) seen in MRID 44082201, parental toxicity as decreased body weight (4-6%), increase in absolute and relative liver weight in F0 females, increase in absolute and relative spleen weight, decrease in absolute uterine weight, and increase in relative liver weight in F1 female adults seen in both studies.

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for d-Phenothrin for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD, PAD, LOC for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short-Term (1-30 days), Intermediate-Term (1-6 months), and Long-Term (> 6 months)	Dermal risk assessment is not needed based on lack of toxicity in a dermal toxicity study at the limit dose of 1000 mg/kg/day and the low dermal absorption (<5%)			
Inhalation Short-Term (1-30 days) and Intermediate-Term (1-6 months) (All populations except children <6 years old)	NOAEL= 0.104 mg/L (26.6 mg/kg/day) For HEC and HED see table 4.5.4.3	UF_A= 3 x UF_H= 10 x FQPA SF= 1x	Residential LOC for MOE = 30	90 Day inhalation toxicity study MRID 41289201 LOAEL = 0.291 mg/L (74.4 mg/kg/day) based on histopathological changes in the nasal turbinates.
Inhalation Short-Term (1-30 days) and Intermediate-Term (1-6 months) (Children <6 years old)	NOAEL= 0.104 mg/L (26.6 mg/kg/day) For HEC and HED see table 4.5.4.3	UF_A= 3 x UF_H= 10 x FQPA SF= 3x	Residential LOC for MOE = 100 for Children <6 years	90 Day inhalation toxicity study MRID 41289201 LOAEL = 0.291 mg/L (74.4 mg/kg/day) based on histopathological changes in the nasal turbinates.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies (TXR 0054233).			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 4.5.4.2. Summary of Toxicological Doses and Endpoints for d-Phenothrin for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD, PAD, LOC for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short-Term (1-30 days) and Intermediate-	Dermal risk assessment is not needed based on lack of toxicity in a dermal toxicity study at the limit dose of 1000 mg/kg/day and the low dermal absorption (<5%)			
Inhalation Short-Term (1-30 days) and Intermediate-Term (1-6 months)	NOAEL= 0.104 mg/L (26.6 mg/kg/day) For HEC and HED see table 4.5.4.3	UF_A= 3 x UF_H= 10 x	Occupational LOC for MOE = 30	90 Day inhalation toxicity study MRID 41289201 LOAEL = 0.291 mg/L (74.4 mg/kg/day) based on histopathological changes in the nasal turbinates.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies (TXR 0054233). Quantification of cancer risk is not required.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 4.5.4.3. Human Equivalent Concentrations and Human Equivalent Dose based on Inhalation Study MRID 41289201 and RRDR Methodology						
Population	**Scenario**	**Tox Duration Adjustment**		**HEC**		**HED**
		hr/day	**day/wk**	**mg/L**	**mg/m^3**	**(mg/kg-day)**
Occupational	Handler	8	5	0.015	14.508	1.373
Residential	Handler	NA	NA	0.019	19.344	0.458
	Outdoor post-application	NA	NA	0.019	19.344	0.526
	Indoor Post-application	NA	7	0.014	13.817	0.327
	Bystander	24	7	0.003	3.454	NA

4.6 Endocrine Disruption

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision for d-phenothrin, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), d-phenothrin is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[5] and includes some pesticides scheduled for Registration Review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors. d-Phenothrin was not included in the EDSP list of 52 chemicals (Tier 1, List 1 or Tier 1, List 2).

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website[6].

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[5] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.

[6] http://www.epa.gov/endo/

4.7 Human Incidents and Epidemiology

Phenothrin is being considered under the FQPA-mandated Registration Review program established to review, on a 15 year cycle, pesticides for which a Re-registration Eligibility Decision has been made. One component of the Agency's Registration Review Program is consideration of human incident data. In conjunction with a human health risk assessment based on other data sources, such human incident data can assist the Agency in better defining and characterizing the risk of pesticides/pesticide products.

In the current IDS analysis, January 1, 2011 to February 10, 2016, there were 19 moderate severity single ai incidents reported to Main IDS (Evans, E. and Recore, S, 7/28/2016). There were 301 additional incidents involving multiple chemicals (including phenothrin) reported to Main IDS. There were 1,737 incidents reported to Aggregate IDS involving phenothrin. The query of SENSOR-Pesticides 1998-2012 identified a total of 421 cases for phenothrin. Of these, 30 cases involve a single a.i.: one case was high in severity, three cases were moderate in severity and 26 cases were low in severity. From January 1, 2011 to December 31, 2015, there were 26 incidents classified as consistent, possibly or probably related to phenothrin exposure. From January 1, 2011 to December 31, 2015, 57 human incident involving phenothrin were reported to NPIC. Of the 57 reported incidents, 26 were classified as consistent, possible or probable and 23 incidents were classified as unlikely related to phenothrin exposure and eight incidents were asymptomatic and considered unclassifiable.

The high numbers of reported incidents are likely related to the fact that pyrethroids are now among the most commonly used pesticides in residential settings (Hudson, 2013). Pyrethroids are much less acutely toxic to humans than many older chemicals including organophosphates. EPA cancelled almost all indoor organophosphate uses and now the pyrethroids have replaced them in many cases for residential insect control, with a variety of pyrethroid products now widely available to consumers. The residential use of pyrethroids increased from less than 1 million pounds used in 2001, when the phase-out began, to 2–4 million pounds used in 2007, after it was completed. Due to this increase in the availability and usage of pyrethroid products, an increase in the numbers of acute illnesses and injuries from pyrethroids is expected. Pyrethroid cases are the most commonly reported incidents in both SENSOR and American Association of Poison Control Centers (AAPCC) (Roberts, 2013) and while the majority are low in severity, EPA continues to monitor the pyrethroid incidents for trends in exposure illness scenarios, symptoms and products.

Although there are a high number of phenothrin incidents reported to IDS and SENSOR-Pesticides, the majority of these incidents were classified as minor severity. Minor severity means that a person alleged or exhibited some symptoms, but they were minimally traumatic, the symptoms resolved rapidly and usually involved skin, eye or respiratory irritation. In addition, we note that there were no deaths associated with phenothrin in the databases reviewed (IDS, SENSOR-Pesticides and NPIC). Further, these phenothrin cases generally involved products containing multiple active ingredients. Incidents involving multiple pesticides are considered to provide less certain information about the potential effects of exposure from a particular pesticide. The Agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be conducted.

5.0 Dietary Exposure and Risk Assessment

Unrefined acute and chronic dietary exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model with the Food Commodity Intake Database (DEEM-FCID™) Version 3.16. This software uses 2003-2008 food consumption data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA).

Dietary risk assessment incorporates both exposure and toxicity of a given pesticide. For acute and chronic dietary assessments, the risk is expressed as a percentage of a maximum acceptable dose (i.e., the dose which HED has concluded will result in no unreasonable adverse health effects). This dose is referred to as the population adjusted dose (PAD). The PAD is equivalent to the reference dose (RfD) divided by the additional Safety Factor, if applied. For acute and non-cancer chronic exposures, HED is concerned when estimated dietary risk exceeds 100% of the PAD.

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

The residue of concern in treated plant commodities is d-phenothrin based on the use pattern which results in inadvertent residues only, field trial data which indicate very low residues (i.e., <0.01 ppm), and the requested 0-day pre-harvest interval (PHI) which provides little time for the formation of metabolites in plant or animal tissues.

5.1.2 Summary of Environmental Degradation

The major route of dissipation of d-phenothrin may be aerobic metabolism (soil and aquatic, with respective half-lives of 22.2 and 36.1 days). The available data appear to indicate that d-phenothrin undergoes photolysis. Early generation pyrethroids are known to undergo photolysis, and d-phenothrin's structural similarity with resmethrin (with an aqueous photolysis half-life on the order of about an hour), indicate that aqueous photolysis may be another route of dissipation for the chemical. On the other hand, however, d-phenothrin dissipated very slowly under anaerobic aquatic conditions (half-life of 173.3 days) and was nearly stable to hydrolysis at all pH's. D-phenothrin partitioned quickly into the sediment in both the aquatic metabolism studies, suggesting a high tendency to bind to soils. D-phenothrin's K_{oc} is 141,000, which makes the chemical immobile according to the Food and Agriculture Organization (FAO) mobility classification. Under field conditions, d-phenothrin dissipated rapidly (half-lives of less than a day), compared to the available laboratory studies, suggesting that a combination of processes may occur under actual use conditions.

The bioconcentration factor for d-phenothrin was 1805 for the whole fish, and the depuration half-life was around 4 days. Of the major degradates of d-phenothrin, only CHO-PH resembles the structure of the parent. However, this degradate was formed under hydrolysis conditions, which are expected to be a minor route of dissipation. Since other degradates have lost the basic backbone structure of parent d-phenothrin, they are believed to be less toxic than the parent.

Therefore, only the parent d-phenothrin was considered for assessment (J. Meléndez, D340776, 9/11/07).

5.1.3 Comparison of Metabolic Pathways

The residue of concern in plants and in water is the parent compound only.

5.1.4 Residues of Concern Summary and Rationale

The residue of concern in treated plant commodities is d-phenothrin based on the use pattern which results in inadvertent residues only, field trial data which indicate very low residues (i.e., <0.01 ppm) and the requested 0-day PHI which provides little time for the formation of metabolites in plant or animal tissues.

The residue of concern in water is d-phenothrin. Of the major degradates of d-phenothrin, only 3-phenoxybenzyl(1R,3R)-2,2-dimethyl-3-formyl-cyclopropanecarboxylate (CHO-PH) resembles the structure of the parent. However, this degradate was formed under hydrolysis conditions, which are expected to be a minor route of dissipation. In general, the overall conclusion of the hydrolysis studies was that the route of dissipation is not important (even though the degradate may have been observed at some point at ≥10%). In addition, this degradate was not observed in the aerobic or anaerobic aquatic metabolism studies, which take into consideration hydrolysis in addition to metabolism. Since other degradates have lost the basic backbone structure of parent d-phenothrin, they are believed to be less toxic than the parent (J. Meléndez, D340776, 9/11/07).

Table 5.1.4 Compounds Included in the Risk Assessment and Tolerance Expression and Tolerance

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression	Tolerance *
Plant	Primary Crop	d-phenothrin	d-phenothrin	0.01 ppm
Livestock	Ruminant	d-phenothrin	NA	NA
	Poultry	d-phenothrin	NA	NA
Drinking Water		d-phenothrin	NA	NA

* End-use product (EP): MULTICIDE® Mosquito Adulticiding Concentrate 2705 (10% d-phenothrin; 0.74 lb ai/gal and 10% piperonyl butoxide; 0.74 lb ai/gal; EPA Reg. No. 1021-1688)

5.2 Food Residue Profile

MGK Company submitted data generated in 2003 and 2004 for residues in/on grass, alfalfa, and leaf lettuce to support the company's petition for use of d-phenothrin on agricultural fields (MRID 4677000, D. Soderberg, 2/20/07). Aerial treatments at 1, 4, and 10x the proposed rate were made by a helicopter at 50 feet elevation. Samples were collected 12, 24, 48 and 72 hours after treatment. An acceptable method was used for quantitation of residues in/on alfalfa, grass, and leaf lettuce. The LC/MS/MS method for d-phenothrin had a limit of detection (LOD) of 2 ppb and a limit of quantitation (LOQ) of 10 ppb. For 1x rate samples collected within 24 hours, alfalfa contained < 2 ppb d-phenothrin residues, while nearly 40% of the grass samples (max 5.0 ppb) and one leaf lettuce sample (5.3 ppb) had detectable, but not quantifiable, residues. By 48 hours all three crops had non-detectable residues at the 1x rate, but one leaf lettuce sample and almost 40% of the grass samples bore detectable residues (2-5 ppb) in the first 24 hours.

Quantifiable residues were also seen at the 10x mosquito adulticide application rate in all three crops 12–48 hours after application, with the maximum residue in any sample being 93 ppb in 12 hour lettuce treated at the 10x rate.

HED does not consider it feasible to have any kind of PHI associated with a Section 3 mosquito adulticide use because growers would often not know the restrictions associated with these applications and may not even be aware that such an application has been made over their crops. Therefore, the possible presence of residues needs to be considered within the first 24 hours after such mosquito adulticide treatments (R. Loranger, D327508, 2/21/07).

Since detectable residues of d-phenothrin were found at 10x the proposed rate (and also at the 1x rate), the criterion recommended by HED Chemistry Science Advisory Committee (Chem SAC) is that a non-food use has not been met. The application over agricultural lands is a food use and tolerances were established on all crops. Although such tolerances would normally be based on crop field trials on numerous representative commodities, HED concluded that the available studies are adequate to set a tolerance of 0.01 ppm (10 ppb) on all crops. HED previously recommended that the proposed Multicide Mosquito Adulticiding Concentrate 2705 label be revised to require a 48 hour interval between applications. This will result in the 1.0 lb ai/A per year restriction on the proposed label being reduced to 0.66 lb ai (183 applications of 0.0036 lb ai) (R. Loranger, 11/07). Instead of imposing this 48 hour interval, the registrant has a label restricting the use at any one site to 0.1 lb ai/A/year.

Although there are no registered food uses, there are uses in the home where food may be exposed e.g., kitchens. Labels for these uses have restrictions to prevent/limit food exposure e.g., "In the home, all food-processing surfaces and utensils should be covered during treatment, or thoroughly washed before use. Cover exposed food." HED did not conduct a quantitative assessment of dietary risk for home uses because, based on label prescriptions most (if not all) food will be stored prior to application, any food not stored will likely be covered, and residuals from surfaces/utensils are expected to be low due to washing and/or insignificant transfer to food. Consequently, food residues are expected to be negligible.

5.3 Water Residue Profile

Monitoring data are not available to assess residues of d-phenothrin in drinking water.

Drinking water residues were previously provided by the Environmental Fate and Effects Division (EFED) (J. Melendez, 9/11/2007). The Tier II Estimated Drinking Water Concentrations (EDWCs) of d-phenothrin were calculated using PRZM/ EXAMS (surface water) and SCI-GROW (ground water). For surface water, the acute value is 0.10 ppb, the chronic value is 0.0407 ppb and the cancer/chronic is 0.0369 ppb. The groundwater screening concentration is 0.0060 ppb.

For dietary exposure assessment, HED has decided to use the water solubility for d-phenothrin (as it has for other pyrethroids). The water solubility of d-phenothrin is a conservative value because it is approximately 100 times as high as the highest drinking water concentration provided by EFED (9.7 ppb vs. 0.10 ppb).

Water residues were incorporated in the DEEM-FCID into the food categories “water, direct, all sources” and “water, indirect, all sources.” The drinking water models and their descriptions are available at the EPA internet site: http://www.epa.gov/oppefed1/models/water/.

5.4 Dietary Risk Assessment

Risk assessments were conducted for dietary (food and water) exposure pathways based on label uses including the use as a mosquito control applied over agricultural fields. The assessments were conducted using Dietary Exposure Evaluation Model with the Food Commodity Intake Database (DEEM-FCID™) Version 3.16. This software uses 2003-2008 food consumption data from the U.S. Department of Agriculture’s (USDA’s) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA). Unrefined acute and chronic dietary and drinking water exposure and risk assessments (tolerance level residues, with 100% crop treated assumed) conclude that for all commodities, the acute and chronic combined food and drinking water risk estimates do not exceed HED’s level of concern. DEEM 7.91 default processing factor were used.

5.4.1 Description of Residue Data Used in Dietary Assessment

Tolerance level residues were assumed for all food/feed commodities. Milk, soy, and livestock commodities were also added to be very conservative.

5.4.2 Percent Crop Treated Used in Dietary Assessment

100% crop treated was assumed for both the acute and chronic assessments, for all food/feed commodities.

5.4.3 Acute Dietary Risk Assessment

As stated above, for acute and chronic assessments, HED is concerned when dietary risk exceeds 100% of the PAD. The DEEM-FCID analyses estimate the dietary exposure of the U.S. population and various population subgroups.

The exposure and risk estimates are not of concern for females 13-49, the only subgroup for which an acute endpoint has been identified. The DEEM acute dietary risk estimate for females 13-49 years of age is <1.0% of the aPAD. See summary Table 5.4.6.

5.4.4 Chronic Dietary Risk Assessment

The results of the chronic dietary exposure analysis are reported in Tables 5.4.4. The general U.S. population and all other population subgroups have exposure and risk estimates that are not of concern. The DEEM chronic dietary risk estimate for children 1-2 years old, the most highly exposed population subgroup, is 5.5% of the cPAD. See summary Table 5.4.6.

5.4.5 Cancer Dietary Risk Assessment

d-Phenothrin was classified as “Not Likely to be Carcinogenic to Humans”, therefore, quantification of cancer risk is not required.

5.4.6 Summary Table

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	Not Applicable		0.000447	<1.0
All Infants (< 1 year old)			0.000952	4.0
Children 1-2 years old*			**0.001315**	**5.5**
Children 3-5 years old			0.000949	4.0
Children 6-12 years old			0.000571	<1.0
Youth 13-19 years old			0.000357	<1.0
Adults 20-49 years old			0.000378	<1.0
Adults 50+ years old			0.000361	<1.0
Females 13-49 years old	0.000773	<1.0%	0.000373	<1.0

* The subpopulation with the highest risk estimate.
aPAD= acute population adjusted dose.
cPAD = chronic population adjusted dose.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

Residential exposures are expected from the existing uses of d-phenothrin. An assessment of all potential residential handler and post-application exposures was conducted with use of a screening-level approach - i.e., the highest application rate or percent ai for each residential exposure scenario.[7]

6.1 Residential Handler Exposure

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are addressed somewhat differently by HED as homeowners are assumed to complete all elements of an application without use of any protective equipment.

The quantitative exposure/risk assessment developed for residential handlers is based on the following scenarios:

- Applying an aerosol spray (broadcast) in indoor and outdoor environments;
- Applying an aerosol spray (perimeter/spot/crack and crevice) in indoor environments;
- Applying a powder to carpet;
- Applying a total release fogger in an indoor environment;
- Applying a shampoo to dogs;
- Applying a spot-on to dogs;
- Mixing/loading/applying a liquid with a manually-pressurized handwand;
- Mixing/loading/applying a liquid with a backpack sprayer;
- Mixing/loading an outdoor residential misting system tank for outdoor environments; and
- Mixing/loading an automatic misting system tank for animal quarters.

Misting systems are application systems designed to spray pesticides in a fine mist to kill mosquitoes and other insects outdoors. Misting systems include spray nozzles that are mounted around the perimeter of a home/barn in the lawn or landscaping, or on parts of the house/barn or fence. The spray nozzles are connected by tubing to a supply of insecticide. Animal barn residential misting systems are application systems designed to spray an aerosolized insecticide to kill mosquitoes and other nuisance insects in and around barns. These systems are fed from a central holding tank and utilize an array of spray nozzles to automatically deliver an aerosolized insecticide at specified intervals throughout the day. The automatic animal barn and outdoor residential misting systems can operate automatically (i.e., at preset intervals) or manually (e.g., remote control or switch) and are often professionally installed and include a service contract to cover maintenance and insecticide refilling. Nevertheless, it is possible for residential homeowners to purchase the pesticide and load the tank (or drums) themselves; therefore, a residential handler assessment was performed. Further, label language for the products supporting misting systems usage do not contain language limiting residential users from loading

[7] I. Nieves, W. Britton. d-Phenothrin: Occupational and Residential Exposure Assessment for Registration Review. D434864. 9/14/16.

the tanks. The basis for this scenario is that handler exposure occurs as the pesticide is poured into the drum by the applicator holding the product container; no applicator scenario is required as misting systems spray the pesticide in the treatment area automatically.

As previously stated, the product label EPA Reg. No. 1021-2576 states, "Not for use in outdoor residential misting systems (indoor and outdoor)." However, while the label clearly states that the product is intended for use in animal quarters, it does not make clear whether this includes residential or commercial animal quarters, or both. Therefore, HED has assessed the automated misting system use as though it were intended for residential application. Outdoor residential misting systems are clearly intended to be used in residential areas and have been assessed as such.

Residential Handler Exposure Data and Assumptions
A series of assumptions and exposure factors served as the basis for completing the residential handler risk assessments. Each assumption and factor is detailed below.

Application Rate:
The registered application rates of d-phenothrin quantitative exposure/risk assessment developed for residential handlers is based on the scenarios listed in Table 3.3.

Unit Exposures and Area Treated or Amount Handled: Unit exposure values and estimates for area treated or amount handled were taken from HED's 2012 Residential SOPs[8]. Recently, an observational study was submitted designed to measure the air concentrations when treating commercial facilities with a ULV fogger (MRID 49602401). These data were reviewed by HED[9] and determined to represent the best available data for assessment of handler ULV fogger usage. Accordingly, these data have been used to assess residential handler exposures from d-phenothrin applications outdoors.

Exposure Duration:
Residential handler exposure is expected to be short-term in duration. Intermediate-term exposures are not likely because of the intermittent nature of applications by homeowners.

Residential Handler Non-Cancer Exposure and Risk Estimate Equations
The algorithms used to estimate exposure and dose for residential handlers can be found in the 2012 Residential SOPs[10].

Summary of Residential Handler Non-Cancer Exposure and Risk Estimates
Table 6.1 provides a summary of residential handler risk estimates from registered residential uses for d-phenothrin. No inhalation risks of concern were identified for any of the residential handler exposure scenarios assessed (an MOE ≥ 30 is not of concern). Estimated inhalation MOEs ranged from 410 to 2,200,000.

[8] Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide
[9] C. Walls. HED Secondary Review of *An Observational Study for the Determination of Air Concentration in the Applicator's Breathing Zone and Deposition of Pyrethrins, Piperonyl Butoxide and MGK 264 from the Use of a ULV Fogger in Various Commercial Applications. 9/2/2016. D428242.*
[10] Available: http://www.epa.gov/pesticides/science/residential-exposure-sop.html

<table>
<tr><th colspan="7">Table 6.1 Residential Handler Non-cancer Exposure and Risk Estimates for Registered Uses of d-Phenothrin.</th></tr>
<tr><th>Exposure Scenario</th><th>Application Equipment/ Method</th><th>Inhalation Unit Exposure (mg/lb ai)</th><th>Application Rate[1]</th><th>Area Treated or Amount Handled Daily[2]</th><th>Inhalation Absorbed Dose[3] (mg/kg/day)</th><th>Inhalation MOE[4]</th></tr>
<tr><td colspan="7">Applicator</td></tr>
<tr><td>Indoor/Outdoor Environment</td><td>Aerosol can (Broadcast Surface)</td><td rowspan="3">3</td><td rowspan="2">0.02 lb ai/16oz can</td><td>1 16oz can</td><td>0.00075</td><td>610</td></tr>
<tr><td rowspan="5">Indoor Environment</td><td>Perimeter/ Spot/ Crack and Crevice with Aerosol Can</td><td rowspan="2">0.5 14oz can</td><td>0.00038</td><td>1,200</td></tr>
<tr><td>Perimeter/ Spot/ Crack and Crevice with Aerosol Can for Bedbugs</td><td>0.0040 lb ai/ 17 oz can</td><td>0.000080</td><td>6,100</td></tr>
<tr><td>Shaker Can (Carpet Powder)</td><td>18</td><td>0.0050 lb ai/16-oz can</td><td>1 16oz can</td><td>0.0011</td><td>410</td></tr>
<tr><td>Total Release Fogger</td><td colspan="5">No quantitative assessment is required since the labels state the applicator must vacate the space immediately following fogger initiation.</td></tr>
<tr><td rowspan="2">Treated Pets</td><td>Shampoo</td><td>0.29</td><td>$8.9x10^{-5}$ lb ai/pet</td><td>2 pets</td><td>0.00000065</td><td>710,000</td></tr>
<tr><td>Spot-On</td><td colspan="5">Inhalation exposures from spot-on applications are considered negligible.</td></tr>
<tr><td colspan="7">Mixer/Loader/Applicator</td></tr>
<tr><td rowspan="2">Outdoor Residential and Recreational Areas</td><td>Manually-Pressurized Handwand</td><td>0.018</td><td rowspan="2">0.00025 lb ai/ft^2</td><td rowspan="3">1200 ft^2</td><td>0.000068</td><td>6,800</td></tr>
<tr><td>Backpack</td><td>0.14</td><td>0.00053</td><td>870</td></tr>
<tr><td>Outdoor Environment</td><td>Handheld ULV Fogger</td><td>8.9</td><td>$8.3x10^{-8}$ lb ai/ft^2</td><td>0.000011</td><td>41,000</td></tr>
<tr><td>Outdoor Residential Misting</td><td rowspan="2">Automatic Misting System</td><td rowspan="2">0.00022</td><td>0.23 lb ai/ 55 gallons</td><td rowspan="2">1 drum (55 gallons)</td><td>0.00000063</td><td>2,200,000</td></tr>
<tr><td>Animal Quarters</td><td>0.48 lb ai/ 55 gallons</td><td>0.00000131</td><td>1,000,000</td></tr>
</table>

[1] Based on registered labels.
[2] Based on HED's 2012 Residential SOPs (http://www.epa.gov/pesticides/science/residential-exposure-sop.html).
[3] Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled per Day ÷ Body Weight (80 kg).
[4] Inhalation MOE = Inhalation HED (0.458 mg/kg/day) ÷ Inhalation Dose (mg/kg/day). LOC=30.

6.2 Residential Post-Application Exposure

There is the potential for post-application exposure for individuals exposed as a result of being in an environment that has been previously treated with d-phenothrin. The quantitative exposure/risk assessment for residential post-application exposures is based on the following scenarios:

- Children 1 to < 2 years old incidental oral (hand-to-mouth and object-to-mouth) post-application exposures from contact with treated turf following broadcast application via aerosol spray;
- Children 1 to < 2 years old incidental oral (hand-to-mouth and object-to-mouth) post-application exposures from contact with treated carpet and hard flooring following indoor broadcast, crack and crevice, total release fogger, and perimeter/spot/bedbug applications;
- Children 1 to < 2 years old incidental oral (hand-to-mouth and object-to-mouth) post-application exposures from contact with powder treated carpet;
- Children 1 to < 2 years old incidental oral (hand-to-mouth and object-to-mouth) post-application exposures from contact with a dog treated via shampoo and spot-on;
- Adults inhalation post-application exposures from activities outdoors following outdoor aerosol space spray usage;
- Adults inhalation post-application exposures from activities outdoors following outdoor residential misting system usage;
- Children 1 to < 2 years old inhalation and incidental oral exposures following outdoor residential misting system usage;
- Adult and children 1 to < 2 years old inhalation exposures following aerial and ground ULV mosquitocide application; and
- Children 1 to < 2 years old incidental oral exposures following aerial and ground ULV mosquitocide application.

The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs[11]. These lifestages are not the only lifestages that could be potentially exposed for these post-application scenarios; however, the assessment of these lifestages is health protective for the exposures and risk estimates for any other potentially exposed lifestages.

<u>Residential Post-application Exposure Data and Assumptions</u>
A series of assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. Each assumption and factor is detailed in the 2012 Residential SOPs[11].

Current HED policy requires assessment for residential post-application exposures of short-, intermediate-, and long-term exposures from spot-on products due to the preventative nature of

[11] Available: http://www.epa.gov/pesticides/science/residential-exposure-sop.html

these products and the potential for extended usage in more temperate parts of the country. The assessment of residential post-application exposures from the d-phenothrin spot-on product are reflective of all duration of exposure.

Dislodgeable Foliar Residue (DFR): In accordance with 40 CFR §158, DFR data are required for all occupational (e.g., crop, nursery, greenhouse use sites) or residential (e.g., ornamental and vegetable gardens, pick your own farms, retail tree farms) uses that could result in post-application exposure to foliage. There is no dermal hazard from post-application exposures to d-phenothrin and, therefore, DFR data are not required at this time.

Turf Transferable Residue (TTR): In accordance with 40 CFR 158, TTR data are required for all occupational (e.g., sod farms, golf courses, parks, and recreational areas) or residential turf uses that could result in post-application exposure to turf. In the absence of chemical-specific TTR data, EPA uses default values. The *2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment* includes an analysis of all TTR data, available at the time, which resulted in the selection of revised liquid and granular default values for the fraction of the application rate available for transfer after a turf application (F_{AR}). These values are based on an analysis of 59 TTR studies performed with the Modified California Roller Method (36 studies using liquids, 11 studies using wettable powders/water dispersible granules, and 12 studies using granules). The liquid results (N=131) indicate a range of F_{AR} values from 0.0005% to 6.1% and the granular results (N=37) indicate a range of 0.00064% to 0.69%. In both the liquid and granular data, a large range of transferability is observed and this variability can potentially be attributable to many factors such as active ingredient; formulation; field conditions in the studies; weather conditions (e.g., humidity); or many other difficult to quantify factors. Although witnessed across multiple chemicals, this range in F_{AR} values is not expected when considering TTR data for a single chemical. HED selected 1% and 0.2% as high-end default values for liquid and granular products, respectively.

Because TTR data are not available for phenothrin, EPA is using cyfluthrin TTR data. TTR data have been submitted for four pyrethroids: cyfluthrin (liquid formulations), cypermethrin (liquid and wettable powder formulations), deltamethrin (liquid formulations), and permethrin (liquid formulations). Cyfluthrin resulted in the highest normalized turf transferable residues out of the available liquid formulation TTR data. These data were discussed in the 2011 Pyrethroid CRA. Due to the similar physiochemical properties among the pyrethroids, cyfluthrin TTR data are recommended for use as a surrogate when chemical-specific TTR data are not available. It is unlikely that chemical-specific TTR data for phenothrin would be needed to further refine exposure assessments or would add appreciably to our general understanding of the availability of turf transferable pesticide residues. Additionally, there is no dermal hazard identified for phenothrin due to the lack of toxicity at the limit dose. Therefore, no TTR data are being required for phenothrin at this time.

Post-application Inhalation Exposure from All Surface Directed Indoor Uses (Broadcast, Crack and Crevice/Spot/Bed Bug): Chemical-specific post-application inhalation exposure data are not available for the proposed surface-directed indoor use of d-phenothrin; however, HED has received and reviewed an Office of Research and Development (ORD) exposure study that was performed in the U.S. EPA's IAQ Research House (D390098). This study simulated crack and crevice applications of four pesticides; two emulsifiable concentrate products applied via a handheld sprayer (permethrin and cypermethrin), one aerosol can product (propoxur), and one gel bait product (fipronil). The application pattern used in this study is considered a reasonable representation of an indoor crack and crevice application, but also can represent other indoor applications such as perimeter (coarse and pinstream) as well as surface directed broadcast uses due to the nature of the applications (applications were made to floor-to-ceiling paneling on three walls of an interior room). Air concentrations of all four chemicals were collected using stationary air samplers suspended 75 cm above the floor in the room of application (the living room) and two other rooms in the test house (the den and master bedroom). Air samples were collected during the application and 1, 1.5, 2, 2.5, 3, 7, 14, 21, 28, and 35 days after application. Permethrin and cypermethrin air concentrations were not found in any measurable quantities in any room in the research house.

Although the data are not chemical specific, the Non-Dietary Exposure Task Force (NDETF) has performed an analysis of all the pyrethroid surface deposition and hand press exposure data that they produced. This analysis shows the exposure data for one pyrethroid can generally be used to represent the entire chemical class. Based on this NDETF analysis and the generally low vapor pressure of pyrethroids, HED believes it is appropriate to use the air concentration data from the ORD study as a surrogate for d-phenothrin when applied as a surface-directed application indoors. HED does not have concerns for d-phenothrin for the post-application inhalation exposure scenario given that all air concentration values were below the limit of quantitation in the ORD study.

Post-application Inhalation Exposure Resulting From Fogger Applications:
Post-application inhalation exposure from the use of indoor foggers is expected to be negligible, since most fogger product labels typically state a period of no-entry following application (usually up to 4 hours), as well as a ventilation period before occupants can return. In addition, due to the low vapor pressure of pyrethroids in general, and the available air concentration data collected from the ORD test house following indoor applications of pyrethroids (D390098), HED does not have concerns for indoor fogger applications of d-phenothrin.

Post-application Inhalation and Incidental Oral Exposures from Residential Misting Systems:
Residential post-application inhalation exposures are expected for adults and children following treatment with residential misting systems. Incidental oral exposures are also expected for children 1 to < 2 years old from contact with d-phenothrin residues that have settled on turf following a pulse, or release, of the misting system. Post-application exposures from residential misting systems are assessed using the methodologies and inputs described in the 2012 Residential SOPs (Outdoor Fogging/Misting Systems and Animal Barn Misting System SOPs). The Animal Barn Misting System SOP recommends input of an active ingredient per single pulse application rate. This single pulse application rate is assumed to occur once hourly during the duration of time the exposed individual spends in the barn (i.e., 4 hours per day for adults, and 2 hours a day for children 3 to < 6 years old). For the d-phenothrin animal quarter automatic misting system use, only a daily maximum application rate (4.8 fl oz/ 1,000 ft^3/day) is provided

on product labeling; i.e., the total amount of active ingredient to not be exceeded over the course of all release intervals in a day. The label does not provide detail of how many pulses per day should be used to release this total, nor does it describe the time of day that the releases should occur. Typically, misting systems are designed so that pulses of active ingredient are released during the time of highest insect activity, during the early morning and late afternoon. In order to determine an active ingredient per pulse release rate appropriate for use with the SOPs, HED has assumed that the label maximum application rate is released over 6 intervals daily; 3 in the early morning and 3 in the late afternoon.

As previously described, the d-phenothrin product label, EPA Reg. No. 1021-2576 contains conflicting language relating to its use in automated misting systems. HED has assessed the automated misting system use as though it were intended for application in residential animal quarters and presented the resulting risks which are of concern. If the label language is clarified to restrict residential animal quarter usage during registration review, then HED will reconsider the need for a residential post-application assessment.

Residential Post-application Indoor Fraction of Residue Available for Transfer (Fai): Consistent with the 2011 Pyrethroid CRA, the assessment of indoor post-application exposures uses the average Fai for all pyrethroids. Chemical-specific data provided by the NDETF were used for the fraction of residue available for transfer (Selim, 2004a; Selim, 2003b; Selim, 2003c; Selim, 2000; Selim, 2002b; Selim, 2002c). The NDETF studies examined the transferability of residues from bare hand-presses on carpets and hard surfaces for deltamethrin, permethrin, and pyrethrins. For carpets, the fraction transferred was 0.03, 0.02 and 0.01 for pyrethrins, permethrin and deltamethrin, respectively. For hard surfaces, the fraction transferred was 0.04, 0.03, and 0.05 for pyrethrins, permethrin, and deltamethrin, respectively. Since the values were so similar across the three chemicals, the average fraction transferred was used for all the pyrethroids in the cumulative assessment: 0.02 for carpets and 0.04 for hard surfaces.

Residential Post-application Indoor Deposited Residue (DepR) Values: Based on pyrethroid-specific data available in the 2012 SOPs, the following approaches/default values were used.

- Broadcast applications: The deposited residue from indoor broadcast applications was determined using a tiered approach. Where possible, deposition (ug/cm^2) was calculated based on application rate. Where deposition could not be calculated, the default residue of 15 μg/cm^2 was used and adjusted for the percent ai.

- Perimeter/Spot/Bedbug applications (coarse): For coarse perimeter/spot/bedbug applications, the default deposited residue value, 2.6 μg/cm^2, was used with no adjustment for percent ai. This value is a combination of the pyrethroid data from Keenan (2007) and esfenvalerate data from Selim (2008) for all pyrethroids.

- Perimeter/Spot/Bedbug applications (pin stream): For pin stream perimeter/spot/bedbug applications, the default deposited residue, 1.5 μg/cm^2, was used with no adjustment for percent ai. This value is a combination of the pyrethroid data from Keenan (2007) and the ORD Test house data (D390098) for all pyrethroids.

- Crack and crevice applications: For crack and crevice applications, the default deposited residue value, 0.4 μg/cm^2, was used with no adjustment for percent ai. This value is a combination of the pyrethroid data from Keenan (2007), the esfenvalerate data from Selim (2008) and the ORD Test house data (D390098) for all pyrethroids.

- Fogger applications: In the 2011 pyrethroid cumulative, the chemical-specific residue for deltamethrin, permethrin, and pyrethrins was used, making an adjustment for the maximum percent active ingredient registered. For pyrethroids without chemical-specific residue data, the average residue value, 5.4 μg/cm^2 for a 0.5% fogger, obtained from the three studies was used, making the same adjustment for maximum percent active ingredient registered.

Residential Post-application from Animal Barn Applications: While barns and stables are “indoors” (i.e., enclosed or semi-enclosed structures), the ORD test house study described above is considered protective because of methodological similarities to “indoor” scenarios and because barns often have significantly more air exchange than standard indoor commercial or residential spaces. Additionally, even though a quantitative residential post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for animal quarter residential handlers. HED considers that handler exposure resulting from application of pesticides inside animal quarters is likely to result in higher exposure than post-application exposure.

Ground-based Truck-Mounted-Foggers (Deposition Fraction): For the ground-based truck mounted fogger ULV applications, a 5% deposition was previously used based on a study conducted by Teitze et al., (*Mass Recovery of Malathion in Simulated Open Field Mosquito Adulticide Tests*; Archives of Environmental Contamination and Toxicology; 26: 473-477; 1994). However, in an analysis from 2013 (C. Peck, D407817, 3/28/2013), the Environmental Fate and Effects Division (EFED) reviewed eight published studies on ground ULV application in which deposition was measured. The studies varied in collection media (i.e., grass clippings and coupons), distance from application or spray head (ranging from 8 meters to 500 meters), and chemical measured (i.e., fenthion, malathion, naled, and permethrin). After considering the available data, HED has determined that an off-target deposition rate of 8.7 percent of the application rate may be used to evaluate ground-based ULV applications (i.e., 8.7 percent of the target application rate deposits on turf). This value is the 90 percent upper confidence limit on the mean and is slightly higher than the mean values from all the data points observed in the studies (7.1%, n= 94). The adjusted application rate for the mosquitocide applications (0.0036 lb ai/A x 0.087 = 0.00031 lb ai/A) was then used to define TTR levels by scaling the available cyfluthrin TTR data (0.010 μg/cm^2 x 0.00031 lb ai/A/0.1 lb ai/A = 0.000034 μg/cm^2).

Ground-based Truck-Mounted Foggers (Airborne Concentrations): In order to calculate airborne concentrations from ULV truck fogger applications, HED used the 2012 Residential

SOPs for Outdoor Fogging/Misting Systems, with minimal modification to the well mixed box (WMB) model. The WMB model allows for the estimation of air concentrations in the breathing zones of adults and children for use in calculating the post-application inhalation exposure to individuals residing in areas being treated by ground application of d-phenothrin. The methodology more accurately accounts for dilution using the WMB model. The WMB model input parameters and the algorithms used to estimate residential post-application exposures can be found in the occupational and residential exposure assessment document (I. Nieves, W. Britton; D434864).

Aerial ULV Mosquitocide Applications (Deposition Fraction and Airborne Concentrations): Deposition and airborne concentrations of d-phenothrin from aerial ULV applications was modeled using the *AGDISP* (version 8.26) model to predict the motion of spray material released from aircraft, to determine the amount of application volume that remained aloft, and the amount of the resulting droplets deposited on the surfaces in the treatment area as well as downwind from the treatment area. The deposition fraction provided by *AGDISP* for d-phenothrin was 1.6 (limited to a maximum deposition of 1.0 for purpose of risk assessment). The aerial off-target deposition rate of 1.0 of the application rate may be used by HED to evaluate aerial ULV applications (i.e., 100% percent of the target application rate deposits on turf). The adjusted application rate was then used to define TTR levels by scaling the available cyfluthrin TTR data (0.010 $\mu g/cm^2$ x 0.0036 lb ai/A/0.1 lb ai/A = 0.00040 $\mu g/cm^2$). No further scaling for deposition was required since the rate is 1.0. The *AGDISP* model also allows for the estimation of air concentrations in the breathing zones of adults and children for use in calculating the post-application inhalation risks to individuals residing in areas being treated by aerial application of d-phenothrin.

Figure 6.2.1.a presents the airborne concentrations for the 1 hour following mosquito adulticide application, and figure 6.2.1.b presents the estimated aerial d-phenothrin residue fraction deposited on turf. The 1 hour air concentrations are calculated for adults and children at breathing heights of 6 feet and 3 feet, respectively.

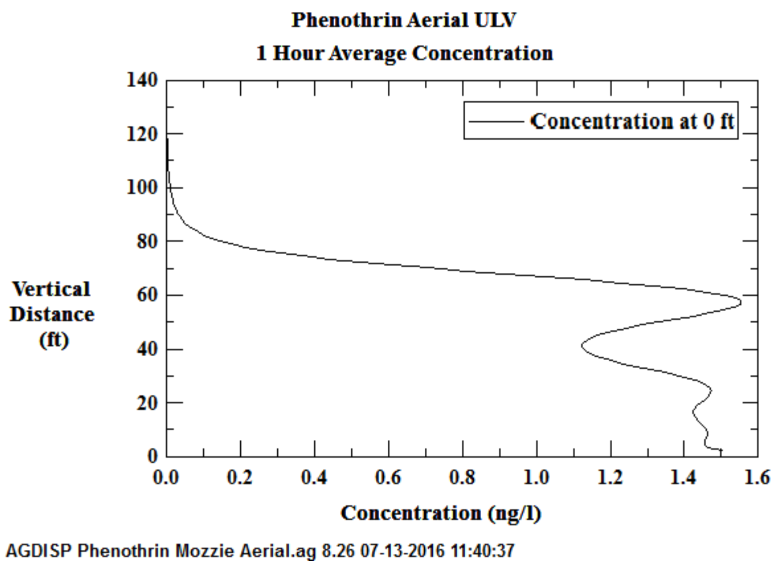

Figure 6.2.1.a Estimated d-phenothrin air concentration at the field edge from aerial treatment of mosquito adulticide at a release height of 100 feet. 1.5 ng/l = 0.0015 mg/m^3 is the concentration at breathing height 6 feet from the ground for adults and 3 feet from the ground for children.

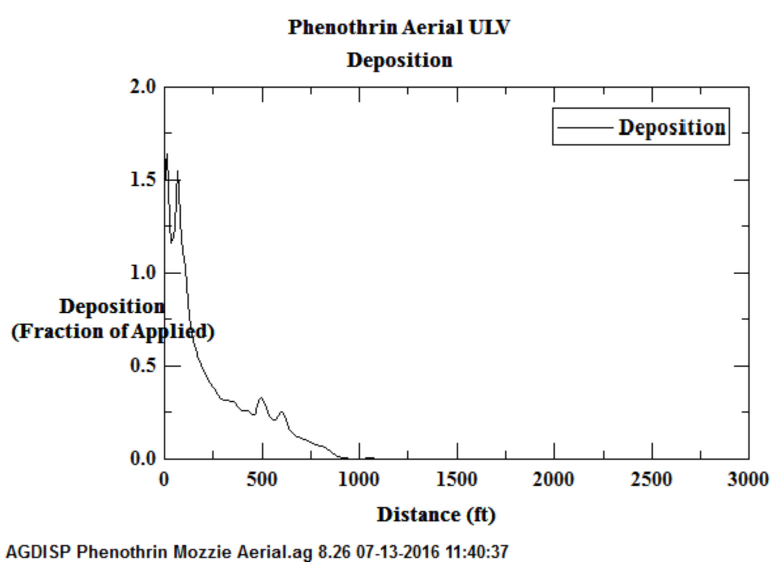

Figure 6.2.1.b Estimated d-phenothrin deposition downwind from the field edge from aerial treatment of mosquito adulticide at release height of 100 feet. Where the fraction of application rate for deposition was determined to be ~1.6, the maximum fraction of 0.99 will be used for the deposition value.

Residential Post-application Non-Cancer Exposure and Risk Equations

The algorithms used to estimate residential post-application exposure and dose can be found in the 2012 Residential SOPs[11].

Combining Exposures/Risk Estimates:
The endpoints for inhalation and incidental oral exposures are not the same; therefore, these exposure estimates have not been combined.

Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates

Table 6.2.1 provides a summary of residential post-application risk estimates from the registered uses of d-phenothrin. Table 6.2.2 provides a summary of residential post-application inhalation exposures to adults and children 1 to <2 years old following ULV aerial and ground mosquitocide applications. Table 6.2.3 provides a summary of residential post-application incidental oral exposures to children 1 to < 2 years old from contact with treated turf following ULV aerial and ground mosquitocide applications. The majority of post-application risks estimated were not of concern (i.e., adult inhalation MOEs ≥ 30; children 1 to < 2 years old and children 3 to <6 years old inhalation MOEs ≥ 100 MOEs; and children 1 to < 2 years old incidental oral MOEs ≥ 300). MOEs not of concern ranged from 340 to 240,000. Residential post-application risks of concern were identified from inhalation exposures in animal quarters following treatment with an automated misting system (i.e., MOEs were 0.79 and 0.57 for adults and children 3 to <6 years old, respectively).

Table 6.2.1. Residential Post-application Non-cancer Exposure and Risk Estimates for d-Phenothrin.					
Lifestage	Post-application Exposure Scenario		Application Rate[1]	Dose (mg/kg/day)[2]	MOEs[3]
	Use Site	Route of Exposure			
Children 1 to <2 Years Old	Indoor Broadcast Application - Carpet	Hand-to-Mouth	0.0030 (0.3%) lb ai/ 16oz can	0.018	2,800
		Object-to-Mouth		0.0071	7,100
	Indoor Perimeter/Spot/Bedbug Application (Coarse) - Carpet	Hand-to-Mouth	0.02 (2.0%) lb ai/ 14oz can	0.0051	9,800
		Object-to-Mouth		0.0020	25,000
	Indoor Perimeter/Spot/Bedbug Application (Coarse) - Hard Flooring	Hand-to-Mouth		0.0026	20,000
		Object-to-Mouth		0.0014	37,000
	Indoor Perimeter/Spot/Bedbug (Pin Stream) Application - Carpet	Hand-to-Mouth		0.0029	17,000
		Object-to-Mouth		0.0012	43,000
	Indoor Perimeter/Spot/Bedbug (Pin Stream) Application - Hard Flooring	Hand-to-Mouth		0.0015	34,000
		Object-to-Mouth		0.00078	64,000
	Indoor Crack and Crevice - Carpet	Hand-to-Mouth		0.00079	64,000
		Object-to-Mouth		0.00031	160,000
	Indoor Crack and Crevice - Hard Flooring	Hand-to-Mouth		0.00039	130,000
		Object-to-Mouth		0.00021	240,000
	Indoor Space Spray - Carpet	Hand-to-Mouth		0.034	1,500
		Object-to-Mouth		0.013	3,700
	Indoor Space Spray - Hard Surfaces	Hand-to-Mouth		0.017	3,000
		Object-to-Mouth		0.0089	5,600
	Indoor Spot (Carpet Powder)	Hand-to-Mouth	0.0050 (0.50%) lb ai/ 16oz can	0.13	380
		Object-to-Mouth		0.11	470
	Bedbug Indoor Perimeter/Spot/Bedbug Application (Coarse) - Carpet	Hand-to-Mouth	0.0040 (0.4%) lb ai/ 17oz can	0.0051	9,800
		Object-to-Mouth		0.0020	25,000
	Bedbug Indoor Perimeter/Spot/Bedbug Application (Coarse) - Hard Flooring	Hand-to-Mouth		0.0026	20,000
		Object-to-Mouth		0.0014	37,000
	Bedbug Indoor Perimeter/Spot/Bedbug (Pin Stream) Application - Carpet	Hand-to-Mouth		0.0029	17,000
		Object-to-Mouth		0.0012	43,000
	Bedbug Indoor Perimeter/Spot/Bedbug (Pin Stream) Application - Hard Flooring	Hand-to-Mouth		0.0015	34,000
		Object-to-Mouth		0.00078	64,000
	Indoor Fogger - Carpet	Hand-to-Mouth	0.020 (2.0%) lb ai/ 4 oz can	0.0057	8,700
		Object-to-Mouth		0.0023	22,000
	Indoor Fogger - Hard Flooring	Hand-to-Mouth		0.0029	17,000
		Object-to-Mouth		0.0015	33,000
	Contact with Treated Pets - Shampoo	Hand-to-Mouth	54 mg ai	0.00046	110,000

Table 6.2.1. Residential Post-application Non-cancer Exposure and Risk Estimates for d-Phenothrin.

Lifestage	Post-application Exposure Scenario		Application Rate[1]	Dose (mg/kg/day)[2]	MOEs[3]
	Use Site	Route of Exposure			
			(Small dog, 20 lbs)		
			135 mg ai (Medium Dog, 50 lbs	0.00049	100,000
			270 (Large Dog, 100 lbs)	0.00063	80,000
	Contact with Treated Pets - Spot-on	Hand-to-Mouth	1010 mg ai (Small Dog, 6 to 15 lbs)	0.017	2,900
			1520 mg ai (Medium Dog, 16 to 30 lbs)	0.015	3,200
			3550 mg ai (Intermediate Dog, 31 to 60 lbs)	0.036	1,400
			5320 mg ai (Large Dog, > 60 lbs)	0.034	1,500
Adult	Outdoor Residential Misting System	Inhalation	$6.4x10^{-8}$ lb ai/ft^3 (No application rate given, calculated)	0.00041	1,300
Children 1 to <2 Years Old		Inhalation		0.0016	340
		Hand-to-Mouth		0.00034	150,000
Adult	Automated Misting System - Animal Quarters	Inhalation	4.8 fl oz/ 1,000 ft^3 / day (0.80 fl oz/ 1,000 ft^3 per release interval)	0.69	**0.79**
Children 3 to <6 Years Old		Inhalation		0.92	**0.57**
		Hand-to-Mouth		0.032	1,500

1 Based on registered labels presented in Table 3.3.
2 Dose (mg/kg/day) algorithms provided in 2012 Residential SOPs (http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 MOE = POD (mg/kg/day) ÷ Dose (mg/kg/day).

Table 6.2.2. Residential Post-application Inhalation Exposure Estimates Resulting from d-Phenothrin Mosquitocide Application		
Population	**Air Concentration Estimate (mg/m^3)[1]**	**MOE[2]**
Aerial ULV (100 ft release height) – AGDISP Model		
Adults	0.0015	13,000
Children 1 to <2 years old		
ULV Truck Fogger – WMB Model		
Adults	0.00046[3]	42,000
Children 1 to <2 years old		

1 Air concentration estimate produced from AGDISP model v8.2.6 at breathing height of adults and children. See the ORE document, D434864, for AGDISP inputs.
2 MOE = HEC (52.7 mg/m^3) ÷ Air concentration (mg/m^3).
3 See the ORE document, D434864, for calculations used to determine the air concentration from ground ULV truck applications.

Table 6.2.3. Residential Post-application Incidental Oral Exposure Estimates Resulting from d-Phenothrin Mosquitocide Application [1]						
Lifestage	**Post-application Exposure Scenario**		**Application Rate (lb ai/A)**	**Exposure Time (hours/day)**	**Incidental Oral Dose (mg/kg/day)**	**MOE**
	Use Site	**Route of Exposure**				
Children 1 to <2 Years Old	Aerial Mosquitocide Application	Hand-to-Mouth	0.0036	1.5	5.4×10^{-5}	920,000
	Ground Mosquitocide Application	Hand-to-Mouth			4.8×10^{-6}	1×10^{7}

1 See the ORE document, D434864 for calculations used to determine the incidental oral exposures from aerial ULV applications.

6.2.1 Residential Risk Estimates for Use In Aggregate Assessment

The recommended residential exposure for use in the children 1 to < 2 years old aggregate assessment is from hand-to-mouth exposure following contact with carpet treated with a d-phenothrin powder product. The MOE (380) is not of concern.

Table 7.2.1. Recommendations for the Residential Exposures for the Phenothrin Aggregate Assessment.									
Lifestage	Exposure Scenario	Dose (mg/kg/day)[1]				MOE[2]			
		Dermal	Inhalation	Oral	Total	Dermal	Inhalation	Oral	Total
Child 1 to < 2 Years Old	Post-application Exposure Following Contact with Carpet Spot Treated with a Powder	N/A	N/A	0.13	**0.13**	N/A	N/A	380	**380**

[1] Dose = the highest dose for each applicable lifestage of all residential scenarios assessed. Total = dermal + inhalation + oral (background dietary +incidental oral (where applicable).
[2] MOE = the MOEs associated with the highest residential doses. Total = 1 ÷ ((1/Dietary MOE) + (1/Dermal MOE) + (1/Inhalation MOE) + (1/Incidental Oral MOE)), where applicable.

6.3 Residential Bystander Post-application Inhalation Exposure

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, additional route-specific inhalation toxicological studies) or further analysis is needed for d-phenothrin.

6.4 Spray Drift

A quantitative spray drift assessment was not conducted because d-phenothrin does not have a potential for spray drift exposures onto residential areas which are not already being considered (i.e., residential post-application assessment of exposures from turf following mosquito adulticide application) and there are no agricultural uses (i.e., no aerial, groundboom or airblast applications).

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risk estimates from three major sources: food, drinking water, and residential exposures. For d-phenothrin, exposures from these pathways should not be aggregated because the toxicity endpoints for these exposure routes are not based on common specific target organ toxicity effects. Therefore, d-phenothrin aggregate risks are from dietary and residential exposures alone.

7.1 Acute Dietary Aggregate Risk

Acute aggregate risk of exposure to d-phenothrin is composed of exposure to residues in food and drinking water alone. The acute dietary exposure analysis included both food and drinking water; therefore, acute aggregate risk estimates are equivalent to the acute dietary risk estimates, as discussed in Section 5.4.3, above. Acute dietary aggregate risk is not of concern for the general U.S. population or any population subgroup (<1.0% aPAD).

7.2 Short- and Intermediate -Term Aggregate Risk

The short- and intermediate-term aggregate is composed of dietary and non-dietary exposures. The recommended residential exposure for use in the children 1 to < 2 years old aggregate assessment is from hand-to-mouth exposure following contact with carpet treated with a d-phenothrin powder product. The total aggregate MOE (380) is not of concern. This exposure scenario is protective of residential exposures of all durations, including long-term exposures from spot-on treated pets.

Table 7.2 Short-Term and/or Intermediate Term Aggregate Risk Calculations							
Population	Short- or Intermediate-Term Scenario						
	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food and Water Exposure mg/kg/day	Residential Exposure mg/kg/day[3]	Total Exposure mg/kg/day[4]	Aggregate MOE (food, water, and residential)[5]
Child 1-<2 years old Post-application Exposure Contact with Carpet Spot Treated with a Powder	50	300	0.17	0.001315	0.13	0.13	380

[1] Level of Concern for Aggregate Risk = 10x (UF_A) x10x (UF_H) x 3x (FQPA SF) = 300
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC
[3] Residential Exposure = [Oral exposure + Dermal exposure + Inhalation Exposure] (Table 6.2.1)
[4] Total Exposure = Avg Food & Water Exposure + Residential Exposure)
[5] Aggregate MOE = [NOAEL / (Avg Food & Water Exposure + Residential Exposure)]

7.3 Chronic Dietary Aggregate Risk

Chronic dietary aggregate risk of exposure to d-phenothrin is composed of exposure to residues in food and drinking water alone. The chronic dietary exposure analysis included both food and drinking water; therefore, chronic aggregate risk estimates are equivalent to the chronic dietary risk estimates, as discussed in Section 5.4.4, above. Chronic dietary aggregate risk is not of concern for the general U.S. population or any population subgroup (5.5% cPAD).

8.0 Cumulative Exposure/Risk Characterization

The Food Quality Protection Act (FQPA) requires the Agency to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. d-Phenothrin is a member of the pyrethroid/pyrethrin common mechanism group (http://www.regulations.gov; EPA-HQ-OPP-2008-0489-0006). The members of this group share the ability to interact with voltage-gated sodium channels ultimately leading to neurotoxicity. The cumulative risk assessment for the pyrethroids/pyrethrins was published on Nov. 9, 2011 and is available at http://www.regulations.gov; EPA-HQ-OPP-2011-0746. d-Phenothrin is not included in the cumulative risk assessment. No cumulative risks of concern were identified allowing the Agency to consider new uses for pyrethroid actives. For information regarding EPA's efforts to evaluate the risk of exposure to pyrethroids, refer to http://www.epa.gov/oppsrrd1/reevaluation/pyrethroids-pyrethrins.html.

9.0 Occupational Exposure/Risk Characterization

9.1 Short- and Intermediate-Term Handler Risk

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed uses. The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

Mixers/Loaders:
- Mixing/loading liquids for Aerial ULV Applications;
- Mixing/loading liquids for Truck-Mounted Ground ULV Applications; and
- Mixing/loading liquids for Outdoor Residential Misting Systems.

Applicators:
- Applying liquids with Aerial Equipment;
- Applying liquids with Groundboom Equipment;
- Applying liquids with Boom Sprayer Equipment; and
- Applying liquids with Truck Mounted Fogger Equipment (Surrogate: Airblast Scenario)

Mixers/Loaders/Applicators:
- Mixing/loading/applying liquids for backpack sprayers (HED considers this scenario to be protective of backpack blowers);
- Mixing/loading/applying liquids for manually-pressurized handwand applications; and
- Mixing/loading/applying liquids for mechanically-pressurized handgun applications.

HED determined that for purposes of assessing the truck mounted fogger scenario for vector mosquito control, the mixing/loading liquid formulations scenario for groundboom and the applying liquid formulation using airblast sprays would serve as surrogate scenarios.

Occupational Handler Exposure Data and Assumptions
A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below on an individual basis.

Application Rates:
The registered application rates for d-phenothrin are listed in Table 3.3.1.

Unit Exposures: It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the AHETF database, the Outdoor Residential Exposure Task Force (ORETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[12]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[13].

Estimates of inhalation exposure were calculated with a "baseline" level of personal protective equipment (PPE) (i.e., no respirator). The proposed d-phenothrin product label direct mixers, loaders, applicators and other handlers to wear long-sleeved shirts, long pants, and shoes plus socks.

Area Treated or Amount Handled:
The area treated/amount handled are based on ExpoSAC Policy 9.1.

Exposure Duration:
HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. Exposure duration is determined by many things, including the exposed population, the use site, the pest pressure triggering the use of the pesticide, and the cultural practices surrounding that use site. It is reasonable to believe that occupational handlers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region).

For d-phenothrin, based on the proposed use, short- and intermediate-term exposures are expected, since there is the potential for multiple applications at the maximum application rate. In addition, both the short-and intermediate-term endpoints are the same; therefore, estimates of short-term exposure/risk are protective of any potential longer-term exposures.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates
Table 9.1 provides a summary of short-/intermediate-term risk estimates from the registered uses of d-phenothrin. No inhalation risks of concern were identified for any of the occupational handler exposure scenarios assessed assuming no respirator (i.e., MOEs are ≥ 30). Estimated inhalation MOEs ranged from 630 to 3,500,000.

Per labeling, human flagging is prohibited. Flagging to support aerial applications is limited to use of the Global Positioning System (GPS) or mechanical flaggers.

[12] Available: http://www.epa.gov/opp00001/science/handler-exposure-table.pdf
[13] Available: http://www.epa.gov/pesticides/science/handler-exposure-data.html

Table 9.1. Short-/Intermediate-Term Occupational Exposure and Risk Estimates for d-Phenothrin. All estimates are at baseline mitigation.						
Exposure Scenario	**Crop or Target**	**Inhalation Unit Exposure (ug/lb ai)[1]**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Inhalation (No Respirator)**	
		Baseline			**Dose (mg/kg/day)[4]**	**MOE[5] LOC=100**
Mixer/Loader						
Aerial ULV	Mosquito Adulticide	0.219 (No Respirator)	0.0036 lb ai/A	7,500 Acres	0.000074	19,000
Truck-Mounted Ground ULV				40 Acres	0.00000039	3,500,000
Outdoor Residential Misting System	Outdoor Environments		0.23 lb ai/ 55 gallons	55 gallons	0.000346	4,000
Automatic Misting System	Animal Quarters		0.48 lb ai/ 55 gallons		0.000723	1,900
Applicator						
Aerial ULV	Mosquito Adulticide	0.0049 (Eng. Controls)	0.0036 lb ai/A	7,500 Acres	0.0000017	830,000
Truck-Mounted Ground ULV (Airblast Surrogate)		4.71 (No Respirator)		40 Acres	0.0000085	160,000
Mixer/Loader/Applicator						
Aerosol Spray	Indoor Broadcast	1,300 (No Respirator)	0.0030 (0.3%) lb ai/ 16-oz can	2 cans	0.0000975	14,000
	Indoor Perimeter/Spot/ Crack & Crevice		0.02 (2.0%) lb ai/ 14-oz can		0.00065	2,100
	Indoor Space Spray					
Powder	Indoor Carpet	17,500 (No Respirator)	0.0050 (0.50%) lb ai/ 16-oz can		0.00219	630
Fogger	Indoor Fogger	N/A	0.020 (2.0%) lb ai/ 4 oz can	No quantitative assessment is required since the labels state the applicator must vacate the space immediately following fogger initiation.		

Table 9.1. Short-/Intermediate-Term Occupational Exposure and Risk Estimates for d-Phenothrin. All estimates are at baseline mitigation.

Exposure Scenario	Crop or Target	Inhalation Unit Exposure (ug/lb ai)[1]	Maximum Application Rate[2]	Area Treated or Amount Handled Daily[3]	Inhalation (No Respirator)	
		Baseline			Dose (mg/kg/day)[4]	MOE[5] LOC=100
Mixer/Loader						
Backpack	Outdoor residential, commercial, recreational areas and in and around horse barns landscaping, turf (lawns, athletic fields, parks, etc.) poultry/livestock house/horse barn/feed lots	30	0.006 lb ai/gallon	40 gallons	0.00009	15,000
Manually-Pressurized Handwand						
Handheld ULV Fogger	Mosquito Adulticide	8.9 (No Respirator)	0.0036 lb ai/A	5	0.002	690

[1] Based on "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (March 2012); includes data from PHED/ORETF/AHETF (level of mitigation: Baseline).
[2] Based on Registered Labels (Table 3.3).
[3] Exposure Science Advisory Council Policy #9.1
[4] Inhalation Dose = Inhalation Unit Exposure (ug/lb ai) x Conversion Factor (0.001 mg/ug) x Application Rate (lb ai/acre or gal or the number of cans per day) x Area Treated or Amount Handled Daily (A or gal/day) /BW (kg).
[5] Inhalation MOE = Occupational Handler HED (1.37 mg/kg/day) / Inhalation Dose (mg/kg/day).

9.2 Occupational Post-Application Risk

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

9.2.1 Occupational Dermal Post-application Risk

Dermal post-application exposure was not quantified since a toxicological dermal endpoint was not selected for d-phenothrin.

9.2.2 Occupational Inhalation Post-application Risk

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (https://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for d-phenothrin.

Although a quantitative occupational post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational/commercial handlers. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios.

Commercial applicators do not typically return to the treated areas after an indoor commercial pesticide application (e.g., animal quarters) and thus an occupational post-application inhalation exposure assessment was not performed for commercial applicators.

10.0 References

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Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for the food use of d-phenothrin are in the following Table. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	-
870.3465 90-Day Inhalation	yes	yes
870.3700a Developmental Toxicity (rodent)	yes	no
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity--Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity--Gene Mutation - mammalian	yes	yes
870.5xxx Mutagenicity--Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity--Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotox. (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotox. Screening Battery (rat)	yes	no
870.6200b 90 Day Neuro. Screening Battery (rat)	yes	no
870.6300 Develop. Neuro	yes*	-
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	yes	yes***
870.7800 Immunotoxicity	yes**	-
Special Studies for Ocular Effects		
Acute Oral (rat)	no	-
Subchronic Oral (rat)	no	-
Six-month Oral (dog)	no	-

* waived (D371723, TXR 0055306)

** waived (TXR: 0056770 and HASPOC TXR: 0056729)

*** Typically, pyrethroids have a low absorption value of ≤ 5% and a high rate of metabolism. This is typical of the pyrethroids, as they are lipophilic, and much of the radioactivity measured in the skin of dermal penetration studies with pyrethroids is captured in the upper dermal layers and not available for absorption or systemic circulation.

A.2 Toxicity Profiles

Table A.2.1. Acute Toxicity Profile – D-phenothrin				
GLN No.	**Study Type**	**MRID**	**Results**	**Toxicity Category**
870.1100	Acute oral [Rat]	40908302 (1987)	LD_{50} > 5000 mg/kg (no deaths)	IV
870.1200	Acute dermal [Rat]	40908303 (1987)	LD_{50} >2000 mg/kg (no deaths)	III
870.1300	Acute inhalation [Rat]	43889301 (1995)	LC_{50} > 2.1 mg/L (no deaths)	IV
870.2400	Acute eye irritation [Rabbit]	40908304 (1988)	Mild irritant	III
870.2500	Acute dermal irritation [Rabbit]	40908304 (1988)	Non-irritating	IV
870.2600	Skin sensitization [Guinea pig]	40908305 (1988)	Not a sensitizer	NA

Table A.2.2. Subchronic and Chronic Toxicity Profile – D-phenothrin		
Guideline No. Study Type	**MRID No (year) Classification Doses**	**Results**
870.3100 90-Day oral toxicity (rat)	40998202 (1983) **Acceptable/guideline** 0, 300, 1000, 3000, 10,000 ppm M: 21, 70, 216, 706 mg/kg/d F: 23, 75, 227, 714 mg/kg/d	**NOAEL** = 70/75 mg/kg/day (both sexes) **LOAEL** = 216/227 mg/kg/day based on increased liver weight, increased lactate dehydrogenase, decreased cholesterol (both sexes).
870.3465 90-Day inhalation toxicity (rats)	41289201 (1989) **Acceptable/guideline** 0, 0.030, 0.104, 0.291, 1.066 mg/L 6 hr./day, 5 days/week for 13 weeks	**NOAEL** = 0.104 mg/L **LOAEL** = 0.291 mg/L based on histopathologic changes in the nasal turbinates in both sexes. Increased absolute thyroid weights (25%) and adrenal weights (21%) and slight histopathologic changes of the thyroid in females at 1.066 mg/L and minor histopathologic adrenal lesions in males at 0.291 and 1.066 mg/L. The· effects on the thyroid and adrenals are of uncertain toxicological significance.
870.3200 21/28-Day dermal toxicity (rats)	41009710 (1989) **Acceptable/guideline** 0, 100, 300, 1000 mg/kg/day	**NOAEL** = 1000 mg/kg/day (HDT) **LOAEL** = not established.
870.3250 5-Week Oral toxicity (mouse)	40998201 (1983) **Acceptable/guideline** 300, 1000, 3000, 10,000 ppm M: 57, 190, 565, 1958 mg/kg/d F: 71, 230, 710, 2339 mg/kg/d	**NOAEL** = 190/230 mg/kg/day **LOAEL** = 565/710 mg/kg/day based on increased liver weight, increased periacinar hepatocytic hypertrophy, decreased kidney weight, and increased alkaline phosphatase.
870.3465 26-Week Oral toxicity (dog)	00148558 (1981) **Acceptable/guideline** 0, 100, 300, 1000 ppm M: 3.02, 9.28, 31.87 mg/kg/d F: 3.14, 9.31, 32.90 mg/kg/d	**NOAEL** = 1000 ppm (31.87 mg/kg/day for males and 32.90 mg/kg/day for females **LOAEL** =. Was not determined. (TXR 0054975).

Table A.2.2. Subchronic and Chronic Toxicity Profile – D-phenothrin		
Guideline No. Study Type	**MRID No (year) Classification Doses**	**Results**
870.3700a Prenatal developmental in (rat)	00153471 and 47452201 (1983) **Acceptable/guideline** 0, 300, 1000 and 3000 mg/kg/day in corn oil GD6-15	**Maternal NOAEL** = 1000 mg/kg/day **LOAEL** = 3000 mg/kg/day based on decreased weight gain, decreased food consumption and increased water consumption. **Developmental NOAEL** = 1000 mg/kg/d **LOAEL** = 3000 mg/kg/day based on decreased fetal weight, increased placental weight and developmental delay (small and immature fetuses).
870.3700a Prenatal developmental in (rabbit)	41230003 (1989) **Acceptable/guideline** 0, 30, 100, 300, 500 mg/kg/d in methylcellulose	**Maternal NOAEL** = 100 mg/kg/day **LOAEL** = 300 mg/kg/day based on decreased weight gain, decreased food consumption. At 500 mg/kg/day, there was an increase in abortions and clinical signs. **Developmental NOAEL** = 30 mg/kg/day **LOAEL** = 100 mg/kg/day based on 1 occurrence of spina bifida (an indicator of neurotoxic effects). At 300 mg/kg/day, one fetus had micropthalmia. At 500 mg/kg/day, 4 fetuses in 3 litters exhibited hydrocephaly, which was outside the historical range for historical controls (5.2% vs. 0.0-3.0% control fetal incidence and 27% vs. 0.0-5.6% control litter incidence), but was not statistically significant. TXR 0054975 A subsequent study conducted at a higher dose (750 mg/kg/day) showed no developmental effects (MRID 49173605, see below; TXR 0056772)
870.3700a Prenatal developmental in (rabbit)	49173605 (2009) **Acceptable/non-guideline** 0, 750 mg/kg/day GD 6-28 in 0.5% methylcellulose	Adverse clinical signs (scant or no feces, soft or liquid feces, ungroomed coat, thin body condition, and dehydration), and transient decreases in body weight gain and food consumption. Maternal deaths and abortions were seen at the only dose tested. This study showed no test substance-related effects on fetal deaths, fetal growth, or developmental malformations or variations, and specifically no evidence of hydrocephalus among 367 fetuses in 48 litters).
870.3800 Reproduction and Fertility Effects (rat)	40276404 (1986) **Acceptable/ guideline** 0, 300, 1000, or 3000 ppm (equivalent to 0, 15, 50, 150 mg/kg bw/day)	**Maternal/Systemic NOAEL** = 50 mg/kg/day **LOAEL** = 150 mg/kg/day based on decreased body weight (4-6%), increase in absolute and relative liver weight in F0 females, decrease in mean body weight of F1 adult males (6%), increase in absolute and relative spleen weight, decrease in absolute uterine weight, and increase in relative liver weight in F1 female adults. **Reproductive/Offspring NOAEL** = 50 mg/kg/day **LOAEL** = 150 mg/kg/day based on slight decreases in litter size, decreases in absolute heart and kidney weights of F2b male offspring, increase in relative liver weight of F2b male and female offspring

Table A.2.2. Subchronic and Chronic Toxicity Profile – D-phenothrin

Guideline No. Study Type	MRID No (year) Classification Doses	Results
870.3800 Reproduction and fertility effects (rat)	44082201 (1995) **Acceptable/guideline** 0, 1000, 3000, 10,000 ppm M: 58.8, 177.2, 581.6 mg/kg/d F: 69.7, 207.9, 664.1 mg/kg/d	**Parental/Systemic NOAEL** = 1000 ppm (58.8 mg/kg/day) **LOAEL** = 3000 ppm (177.2 mg/kg/day) based on reductions in body weight and food consumption, and increased liver weights and microscopic hepatocellular changes. **Reproductive/Offspring NOAEL** = 1000 ppm (58.8 mg/kg/day) **LOAEL** = 3000 ppm (177.2 mg/kg/day) based on decreases in mean pup weights.
870.4100a Chronic toxicity (rat)	40276405 (1987) 0, 300, 1000, 3000 ppm M/F: 15, 50, 150 mg/kg/d **Unacceptable/guideline** **Dosing was not considered adequate based on a lack of clear toxicity in the high dose groups**	**NOAEL** = 50 mg/kg/day **LOAEL** = 150 mg/kg/day based on decreased weight gain in females, increased relative liver weight in males, increased cystic dilatation of sinuses in mesenteric lymph nodes in males, and increased periacinar hepatocytic hypertrophy in liver in males.
870.4100b Chronic toxicity (dog)	40276401 (1987) **Acceptable/guideline** 0, 100, 300, 1000, 3000 ppm M: 2.69, 8.24, 27.66, 80.19 mg/kg/d F: 2.63, 7.07, 26.77, 79.83 mg/kg/d	**NOAEL** = 8.2/7.1 mg/kg/day **LOAEL** = 27.7/26.8 mg/kg/day based on hepatocellular hypertrophy, focal degeneration in adrenal cortex (both sexes). Goss necropsy examinations of liver and adrenal glands did not reveal any lesions.
870.4300 Combined Chronic Toxicity/ Carcinogenicity (rat)	43927001 (1995) **Acceptable/guideline** 0, 1000, 10,000, 20,000 ppm M: 51, 531, 1116 mg/kg/d F: 63, 653, 1351 mg/kg/d	**NOAEL** = 51/63 mg/kg/day **LOAEL** = 553/653 mg/kg/day based on clinical signs of toxicity, decreases in body weight gain, feed efficiency, triglycerides, phospholipids, alpha-2-globulin, urinary pH, and specific gravity and increases in serum enzymes, A/G ratio, posterior capsular opacity, liver weights and liver histopathology. The CARC classified d-phenothrin as “not likely to be carcinogenic to humans”
870.4300 Carcinogenicity (mouse)	40276402 (1987) **Acceptable/guideline** 0, 300, 1000, 3000 ppm 45 mg/kg/d, 150 mg/kg/d, 450 mg/kg/d	**NOAEL** = 45 mg/kg/day (males) **LOAEL** = 150 mg/kg/day based on increased liver weight and decreased kidney weight (males). NOAEL = 150 mg/kg/d (females) LOAEL = 450 mg/kg/d based on decreased body weight gains, increased liver weight and increased kidney weight (females). (no) evidence of carcinogenicity
Gene Mutation 870.5100 S. typhimurium and E. coli. Sumitomo Chemical Co. study ET-10-0068	00148559 (1981) **Acceptable/guideline** Up to 5000 µg /plate (limit dose)	D-phenothrin was not mutagenic both with and without metabolic activation (S-9) in Salmonella typhimurium strains TA 98, TA100, TA1535, TA1537, TA1538 and E. coli WP-2uvrA gene mutation
Cytogenetics 870.5375 in vitro chromosome Chinese hamster ovary (CHO) cell assay. Hazleton Labs study 10593-0-437	41009711 (1989) **Acceptable/guideline**	Negative for inducing chromosome aberrations in CHO cells exposed with and without S-9 up to cytotoxic or precipitating dose levels

Table A.2.2. Subchronic and Chronic Toxicity Profile – D-phenothrin

Guideline No. Study Type	MRID No (year) Classification Doses	Results
Cytogenetics 870.5375 in vitro chromosome Chinese hamster ovary (CHO) cell assay. Sumitomo Chemical Co. MUT-85091	00160488 (1986) **Acceptable/guideline**	Negative for inducing chromosome aberrations in CHO cells exposed both with and without metabolic activation (S-9) up to cytotoxic or precipitating dose levels
Cytogenetics 870.5395 in vivo mouse cytogenetic assay. Sumitomo Chemical Co. ET-10-0072	00148561 (1981) **Acceptable/guideline**	No clastogenic response in bone marrow of male mice administered a single intraperitoneal injection up to a level (10,000 mg/kg) which was well above the limit dose of 2,000 mg/kg
In vitro DNA damage in in human peripheral blood lymphocytes and in human hepatocytes	Nagy *et al* (2014)* **Acceptable/non-guideline** Genotoxicity was evaluated by the comet assay modified with formamidopyrimidine DNA-glycosylase post-treatment for the detection of oxidative base-damage in DNA. Cytotoxic potential assessed by use of combined fluorescence viability staining.	D-phenothrin induced statistically significant, dose-dependent DNA damage in the absence of marked cytotoxicity at concentrations higher than 20 µM and 50 µM in human blood peripheral lymphocytes and hepatocytes, respectively. Oxidative DNA damage could also be detected in the two cell types, although this did not reach statistical significance.
Other Effects 870.5550 in vitro unscheduled DNA synthesis (UDS) Life Science Research 340-M-04284	00160489 (1984) **Acceptable/guideline**	Did not induce significant increases in UDS in HeLa cells up to 4000 µg/ml
870.5200 Neurotoxicity study (rat)	00148740 (1978) **Unacceptable/non-guideline**	not neurotoxic when administered at 500 mg/kg/day for 5 consecutive days
870.6200a Acute Neurotoxicity study (rat)	47593101 (2008) **Acceptable/guideline** a single oral (gavage; 5 mL/kg) dose of Sumithrin (97% a.i) in corn oil at 0, 200, 600, or 2000 mg/kg (limit dose).	**NOAEL** = 2000 mg/kg **LOAEL >** 2000 mg/kg No compound-related effects on mortality, clinical signs of toxicity, body weight, body weight gain, food consumption, FOB parameters, motor activity, absolute or relative (to body) brain weight, or gross or neuropathology were observed at any dose in either sex.
870.6200b Subchronic Neurotoxicity study (rat)	49173604 (2010) **Acceptable/guideline** 0, 1000, 3000, 10,000, or 20,000 ppm of d-phenothrin (96.8% purity) M: 0**,** 72.9, 208.2, 726.9, and 1456.0 mg/kg /day F: 0, 75.9, 230.3, 738.6, and 1502.1 mg/kg /day	**Systemic Toxicity:** ♂ **NOAEL** = 10,000 ppm (727 mg/kg/d) **LOAEL** = 20,000 ppm (1456 mg/kg/d) based on decreased body weight gain (↓12%) from days 1-8. ♀ **NOAEL** = 3,000 ppm (230 mg/kg/d) **LOAEL =** 10,000 ppm (739 mg/kg/d) based on decreased body weight (↓11%) on day 92 and decreased body weight gain (↓29%) from days 1-92. **Neurotoxicity**: No adverse effects in the neurotoxic measures were reported at the highest dose tested.

Table A.2.2. Subchronic and Chronic Toxicity Profile – D-phenothrin		
Guideline No. Study Type	**MRID No (year) Classification Doses**	**Results**
870.6300 Developmental neurotoxicity	The Agency has reviewed existing pyrethroid DNT data for six pyrethroids in 2010 (D371723, 1/20/10, TXR 0055306) and concluded that the DNT is not a particularly sensitive study for comparing the sensitivity of young and adult animals to pyrethroids. Additionally, the degree of concern for these effects in infants is low because the rat reproductive and offspring effects have clearly defined NOAEL/LOAELs and the POD selected for risk assessment is protective of these effects. Based on this review a DNT study is not required for d-phenothrin.	
870.7485 Metabolism and pharmacokinetics (species)	40276403 (1987) **Acceptable/guideline**	Following single low dose (4 mg/kg), single high dose (200 mg/kg) and following 14 days repeated administration at 4 mg/kg, about 96-100% of C^{14} was excreted in urine and feces in about 7 days. More than 90% of the excreted radioactivity for both sexes and for both the cis and trans isomer was collected within the first two (2) days for each dose group (low, high, repeated) Residues in tissues at 7 days were quite low, with fat having the highest levels. Most urinary metabolites were cleaved esters (major metabolite was 4'OH-PB acid sulfate). Most fecal metabolites were esters (i.e., not cleaved). Metabolites were conjugated with glucuronide, sulfuric acid or glycine. No sex differences were noted.
870.7600 Dermal Penetration	Typically, pyrethroids have a low absorption value of ≤ 5% and a high rate of metabolism. This is typical of the pyrethroids, as they are lipophilic, and much of the radioactivity measured in the skin of dermal penetration studies with pyrethroids is captured in the upper dermal layers and not available for absorption or systemic circulation. MRID 46382501	
870.7800 Immunotoxicity	waived (TXR: 0056770 and HASPOC TXR: 0056729)	
In vivo Endocrine effects	Yamada *et al* (2003)** estrogenic or (anti-) androgenic effects of d-phenothrin in the uterotrophic and Hershberger assays. interaction of d-phenothrin (0, 100, 300 or 1000 mg/kg per day, p.o.) with estrogen- or androgen-mediated mechanisms using in vivo short-term assays.	Potential estrogenic effect of d-phenothrin was evaluated by means of 3-day uterotrophic assay using immature Crj:CD(SD)IGS rats (20 days of age). No increase in uterine weight (wet or blotted) was observed following oral exposure to d-phenothrin. Reference control ethinyl estradiol (0.001 mg/kg per day) showed a significant effect. d-Phenothrin was administered by oral gavage for 10 days to castrated male Crj:CD(SD)IGS rats (7 weeks of age, rats were castrated at 6 weeks of age) with or without co-administration of 0.2 mg/kg per day testosterone propionate (subcutaneous injection on the dorsal surface). Reference controls of methyltestosterone and p,p'-DDE (100 mg/kg per day) provided significant effects in this assay protocol, whereas d-phenothrin did not show any androgenic or anti-androgenic effects. **Conclusion**: d-phenothrin exhibited no potential to cause adverse estrogenic or (anti-)androgenic effects even at dose of 1000 mg/kg per day, the limit dose designated in the current draft protocol by the OECD. D-Phenothrin was not included in the EDSP list of 52 chemicals.

Table A.2.2. Subchronic and Chronic Toxicity Profile – D-phenothrin

Guideline No. Study Type	MRID No (year) Classification Doses	Results
In vitro Endocrine effects	Garey and Wolff. 1998.*** Estrogenic and antiprogestagenic Activities of Pyrethroid Insecticides. Biochemical and Biophysical Research Communications 251: 855–859	Four pyrethroids, fenvalerate, **sumithrin**, *d-trans* allethrin, and permethrin were tested for estrogen and progesterone agonist/antagonist activities using the Ishikawa Var-I human endometrial cancer cell line and the T47D human breast cancer cell line. Both cell lines produce alkaline phosphatase as an indicator of hormonal activity. Fenvalerate and sumithrin demonstrated significant estrogenicity; at concentrations of 10 mM, these compounds achieved maximal activities comparable to that of 10 nM 17a-ethynylestradiol in Ishikawa Var-I cells. None of the four compounds showed statistically significant estrogen antagonist activity or acted as progestins. However, fenvalerate and *d-trans* allethrin significantly antagonized the action of progesterone in T47D cells.

* http://ac.els-cdn.com/S138357181400134X/1-s2.0-S138357181400134X-main.pdf?_tid=f6751fbc-c8ee-11e5-a84e-00000aab0f02&acdnat=1454336616_a453cc6cd71a32f727d00c43001fe517: Evaluation of the genotoxicity of the pyrethroid insecticide d-phenothrin. Mutat Res Genet Toxicol Environ Mutagen. 2014, Aug; 770:1-5

** http://ac.els-cdn.com/S0300483X02007503/1-s2.0-S0300483X02007503-main.pdf?_tid=e06d3cc6-c8f4-11e5-8a27-00000aacb362&acdnat=1454339156_a6b18426d0cd2595a65053f0b94980d2 : Lack of estrogenic or (anti-)androgenic effects of d-phenothrin in the uterotrophic and Hershberger assays. Toxicology 186 (2003) 227-239.

*** http://ac.els-cdn.com/S0006291X98995699/1-s2.0-S0006291X98995699-main.pdf?_tid=02457fcc-f742-11e5-bb09-00000aacb35f&acdnat=1459430038_4253def60eb72bb84f3cc7a0184d30c4 Garey and Wolff. 1998.***
Estrogenic and antiprogestagenic Activities of Pyrethroid Insecticides. Biochemical and Biophysical Research Communications 251: 855–859

A.3 Hazard Identification and Endpoint Selection

A.3.1 Acute Reference Dose (aRfD) - Females age 13-49

Study Selected: Developmental Study-Rabbits

MRID No.: 41230003

Executive Summary: In a developmental toxicity study (MRID 41230003) Sumithrin (94.1% a.i., lot #61001) was administered to 20 New Zealand White rabbits in 5 mL of a 0.5% aqueous methylcellulose vehicle by gavage at dose levels of 0 (vehicle control), 30, 100, 300, or 500 mg/kg bw/day from gestation days (GD) 7-19. Animals were sacrificed on GD 29.

One unscheduled maternal death of unknown cause occurred on GD 20 at 300 mg/kg bw/day. Maternal toxicity presented at 500 mg/kg bw/day as increased incidence of abortions and clinical signs (e.g. decreased defecation/urination, green staining of urogenital fur). Significant ($p<0.05$) decreases in food consumption (↓53-86%) and body weight gain were observed for 500 mg/kg bw/day animals compared to controls. Reduced food consumption (↓81-85%) and body weight gain in 300 mg/kg bw/day animals were not statistically significant, but were considered biologically meaningful. No differences in cesarean parameters were observed for any treatment groups. Gross pathology showed accentuation of the lobular markings of the liver and dark red areas in the stomach for all Sumithrin-treated animals, but these effects were not dose-dependent. Also, 1 dam had pale areas on the kidneys at 100 mg/kg bw/day and 1 dam had fluid-filled abdominal regions at 500 mg/kg bw/day. The maternal LOAEL is 300 mg/kg bw/day, based on decreased body weight gain and food consumption. The maternal NOAEL is 100 mg/kg bw/day.

Developmental toxicity in pups presented as malformations. At 100 mg/kg/day, there was 1 occurrence of spina bifida, which was considered an indicator of neurotoxic effects. At 300 mg/kg/day, one fetus had micropthalmia. At 500 mg/kg/day, 4 fetuses in 3 litters exhibited hydrocephaly, which was outside the historical range for historical controls (5.2% vs. 0.0-3.0% control fetal incidence and 27% vs. 0.0-5.6% control litter incidence), but was not statistically significant. There were no malformations in the 30 mg/kg/day group that were considered to be treatment-related. There were no effects of Sumithrin treatment on other endpoints of developmental toxicity. The developmental LOAEL is 100 mg/kg bw/day, based on neurodevelopmental defects. The developmental NOAEL is 30 mg/kg bw/day.

<u>Dose and Endpoint for Risk Assessment:</u> The developmental NOAEL of 30 mg/kg/day based on the presence of neurodevelopmental effects at the LOAEL of 100 mg/kg/day.

<u>Comments about Study/Endpoint/Uncertainty Factors:</u> The rabbit developmental study provides the lowest acute toxicity finding (developmental effect) of any available study. The total uncertainty factor is 100 (10x interspecies extrapolation, 10x intraspecies variation, 1x FQPA SF).

$$\mathbf{aRfD\ (females\ 3-49\ years\ old)} = \frac{\mathbf{30\ mg/kg\ (NOAEL)}}{\mathbf{100\ (UF)}} = \mathbf{0.3\ mg/kg}$$

A.3.2 Acute Reference Dose (aRfD) - General Population. An acute RfD for the general population or any population subgroups was not selected because no effect attributable to a single (or few) day(s) oral exposure was observed in animal studies.

A.3.3 Chronic Reference Dose (cRfD)

<u>Study Selected:</u> Chronic Feeding-Dog

<u>MRID No.:</u> 40276401

<u>Executive Summary</u>: In a chronic toxicity study (MRID 40276401) Sumithrin (92.7% a.i., Lot No. 41101) was administered to pure bred beagle dogs 4/sex/dose in the diet at dose levels of 0, 100, or 300, 1000, or 3000 ppm at doses equivalent to 0, 2.69/2.63, 8.24/7.07, 27.66/26.77 or 80.19/79.83 mg/kg bw/day in males/females for 0-52 weeks.

There were no unscheduled deaths. There were no treatment-related clinical or ophthalmological signs. There were no treatment-related changes in body weight or body weight gain. Also, there were no treatment-related changes in food consumption or food efficiency. Hematological signs of anemia (decreased RBC, hemoglobin, and hematocrit) and decreased serum albumin and total protein were observed at 3000 ppm in males and females. Increased absolute and relative (to body weight) liver weights were observed at 3000 ppm in females. Also, diffuse heptaocellular enlargement (minimum to slight) was observed at 3000 ppm in 4/4 males and 3/4 females and at 1000 ppm in 1/4 males. In the adrenal cortex, increased focal degeneration with acicular crystalline material at 3000 ppm was observed in 3/4 males and 1/4 females, while at 1000 ppm, this effect was present in 1/4 males. No other treatment-related gross or histopathologic effects were observed. **The LOAEL is 27.7 mg/kg/day in males and 26.8 mg/kg/day in females (1000 ppm), based on hepatocellular enlargement in the liver and focal degeneration in the adrenal cortex of both sexes. The NOAEL is 8.2 mg/kg/day in males and 7.1 mg/kg/day in females (300 ppm).**

Dose and Endpoint for Risk Assessment: The systemic NOAEL of 7.1 mg/kg/day (300 ppm) based on hepatocellular enlargement in the liver and focal degeneration in the adrenal cortex in both sexes at the LOAEL of 26.8 mg/kg/day (1000 ppm).

Comments about Study/Endpoint/Uncertainty Factors: The chronic toxicity study in dogs provides the lowest NOAEL/LOAEL (7.1/26.8 mg/kg/day) for systemic effects of any available chronic study. An uncertainty factor of 100 (10x for interspecies extrapolation, 10x for intraspecies variation is applied for general population excluding children <6 years old. For juvenile susceptibility a 3X uncertainty factor is added for children <6 years old.

$$\textbf{chronic RfD (General Population)} = \frac{\textbf{7.1 mg/kg (NOAEL)}}{\textbf{100 (UF)}} = \textbf{0.07 mg/kg}$$

$$\textbf{chronic RfD (children} < \textbf{6 years old)} = \frac{\textbf{7.1 mg/kg (NOAEL)}}{\textbf{300 (UF)}} = \textbf{0.02 mg/kg}$$

A.3.4 Incidental Oral Exposure (Short- and Intermediate-Term)

Study Selected: 2-generation reproduction study-rat

MRID No.: 40276404 and MRID 440482201

MRID 40276404

Executive Summary: In a 2-generation reproduction study (MRID 40276404) Sumithrin (92.9%, Lot No. 21005) was administered to 30 Sprague-Dawley rats/sex/dose (P generation) in the diet at dose levels of 0, 300, 1000, or 3000 ppm (equivalent to 0, 15, 50, 150 mg/kg bw/day) for 13 weeks before mating to produce F1a litters. After weaning and following a 10 day rest period on the diet, the P generation was again mated to produce the F1b litters. Thirty rats/dose/sex from the F1 generation were selected at random and fed for 13 weeks prior to mating and producing the F2 generation. Following a 10 day rest period on the diet after weaning, the F1 generation was again mated to produce the F2b generation.

There was no treatment-related mortality in the P, F1, or F2 generations. Also, there were no clinical signs of toxicity in any generation, except for about 60 percent of all P males (control and treated), which showed signs of infection by an SDA-type virus during Week 21. This infection did not affect the study.

There were no treatment-related effects in precoital interval, mating, conception rate, and fertility index in the P generation and no effects on the P female estrus cycles. There were no compound-related effects in food or water consumption for the P generation. However, there was a statistically significant decrease (↓4-6%) in body weight (compared to controls) for P females at 3000 ppm. Also, absolute and relative liver weights were increased in 3000 ppm P females and were considered compound related. Statistically significant increases in cystic thyroglossal duct remnants and yellow pigment in the suspensory ligament of the uteri of P females at 3000 ppm were observed, but the relationship to treatment is equivocal. **The parental systemic LOAEL is 3000 ppm (150 mg/kg bw/day) based on decreased body weight and increased absolute and relative liver weight in P females, decreased body weight of F1 adult males, and increased absolute and relative spleen weight and increased relative liver weight with decreased absolute uterine weight in F1 adult females. The parental systemic NOAEL is 1000 ppm (50 mg/kg bw/day)**.

There was a slight decrease in the F1b litter size at 3000 ppm, but the relationship to treatment was equivocal. F1 males had a decrease (↓6%) in body weight during the growth phase that was not statistically significant but was considered biologically important. Also, 3000 ppm F1 males had statistically significant decreases in terminal body weight and absolute heart and kidney weights and increases in relative liver and brain weights compared to controls. There were also increases in the relative and absolute liver weights of the F1 females and F2b male and female weanlings. There were no differences in food or water consumption for F1and F2 animals. There were no effects on body weight, organ weights, or histopathology in F2 animals. No effects on estrus cycles, fertility index, gestation length, live birth index, viability index, lactation index, sex ratio, or litter size was observed for F1 and F2 animals, and physical development was normal. However, for adult F1 females, a significant increase in absolute and relative spleen weight was seen at 3000 ppm. Also, absolute uterine weight was significantly decreased at 1000 ppm and 3000 ppm with relative uterine weight significantly decreased at 1000 ppm. These effects on spleen and uterine weights were considered compound-related. There was a decrease in body weight for F2b pups (↓7.2%) on Day 25 that was not statistically significant, but relationship to treatment was equivocal. **The offspring LOAEL is 3000 ppm (150 mg/kg bw/day), based on decreased F1b litter size, decreased absolute heart and kidney weights of F2b males, and increased relative liver weights of F2b males and females. The offspring NOAEL is 1000 ppm (50 mg/kg bw/day).** No unequivocal evidence of reproductive toxicity was observed.

MRID 44082201

In a 2-generation reproduction study (MRID 44082201) D D-phenothrin (100% a.i.) was administered in the diet to 30 Sprague Dawley rats/sex/dose at dose levels of 0, 1,000, 3,000, or 10,000 ppm (equivalent to doses of 0, 58.8, 177.2, or 581.6 mg/kg/day in P males; 0, 67.6, 204.6, or 734.2 mg/kg/day in F1 males; 0, 69.7, 207.9, or 664.1 mg/kg/day in P females; and 0, 78.3, 241.7, or 833.7 mg/kg/day in F1 females). Exposure to P animals (30/sex/dose) began at approximately 53-54 days of age and lasted for 83 days prior to mating to produce F1 pups. Upon weaning, F1 pups (30/sex/dose) selected to become parents of the F2 generation were fed D D-phenothrin in test diets at the same concentration their dam received. F1 animals were given test diets for 92 days prior to mating. All animals were mated on a 1:1 ratio.

Parental toxicity of D D-phenothrin was observed at 3,000 and 10,000 ppm. At 10,000 ppm, treatment - related reductions (p=<0.05 or 0.01) in body weights were observed in P females decreased (5-10%), F1 males decreased (16-35%), and F1 females decreased (17-32%) during premating. Also during premating, decreased overall body weight gains were observed in the high-dose P females (p=<0.0l) decreased (25%), the F1 females decreased (11%, p=<0.01) and the F1 males decreased (12%). During gestation, treatment-related reductions (days 0-20; p=<0.05-0.0l) in body weights were observed in the 10,000 ppm P females decreased (10-12%) and F1 females decreased (14-17%). In the 10,000 ppm P females, overall body weight gain during gestation was decreased (15%, p=<0.01). During lactation, body weights were reduced in the 10,000 ppm P decreased (12-17%, p=<0.01) and F1 decreased (15-19%, p=<0.01) females. Reductions decreased (18-20%, p=<0.01 or 0.05) of relative and absolute food consumption were observed at the outset of the study in the 10,000 ppm animals which were attributed to taste aversion. Reduced absolute and relative food consumption were also frequently observed in P females decreased (15-18, p=<0.05 or 0.01) during most of the premating period. Absolute food consumption was reduced (p=<0.05-0.01) throughout the premating period in F1 males decreased (7-26%) and females decreased (8-22%).

At necropsy, treatment-related reductions in terminal body weights were observed in the high-dose F1 males decreased (16%, p=<0.01) and females decreased (15%, p=<0.01). Treatment-related increases in relative liver weights were observed in the 10,000 ppm P males increased (20%, p=<0.01); P females increased (59%, p=<0.01); F1 males increased (22%, p=<0.01), and F1 females increased (38%, p=<0.0l). Microscopic examination of liver tissue revealed hepatocellular hypertrophy with minimal to slight focal bile duct proliferation in the 3,000 and 10,000 ppm F1 animals. Hepatocellular hypertrophy was also present in the 3,000 and 10,000 ppm P females, however, bile duct proliferation was noted only in the 10,000 ppm P females.

At 3,000 ppm, treatment-related reductions (p=<0.05 or 0.01) in mean body weights were observed in P females decreased (4-6%), F1 males decreased (6-9%), and F1 females decreased (7-12%) during premating. During premating, decreased overall body weight gains were observed in the mid-dose P females (p=<0.0l) decreased (13%) and in the mid-dose F1 females decreased (8%, p=<0.05). Treatment-related reductions (p=<0.05- 0.01) in body weight were also observed in the P and F1 3,000 ppm females during gestation decreased (6-10%), and lactation decreased (5-9%; F, females only). At necropsy, treatment-related reductions in terminal body weights were observed in F1 males and females decreased (5%, p=<0.05-0.0l). Treatment-related increases in relative liver weights that were accompanied by microscopic evidence of focal hepatocellular hypertrophy and bile duct proliferation were observed in the 3,000 ppm P females increased (20%, p=<0.0l) and F1 females There were no treatment-related mortalities or treatment-related effects on reproductive parameters or function. There were no treatment-related clinical signs of toxicity.

The LOAEL for parental systemic toxicity is 3,000 ppm based on reductions in body weights and food consumption, and increased liver weights and microscopic hepatocellular changes. The parental systemic NOAEL is 1,000 ppm.

Reproductive toxicity of D D-phenothrin was evident at 3,000 and 10,000 ppm. At 10,000 ppm, treatment-related reductions in mean body weights were observed in the F1 decreased (13-38%, p=<0.01) and F2 decreased (13-28%, p=<0.01) pups. A treatment-related increase in mortality was also noted in F1 generation pups during days 2 through 4 (2 controls died vs. 6 mid-dose females and 9 high-dose females). At 3,000 ppm, treatment-related reductions in mean body weights were also observed in the F1 decreased (6-12%, p=<0.01) and F2 decreased (9-11%, p=<0.0l) pups.

The LOAEL for reproductive toxicity is 3,000 ppm based on decreases in mean pup weights (13-38%). The reproductive NOAEL is 1,000 ppm.

This study is acceptable, guideline and satisfies the guideline requirement for a 2-generation reproductive study (OPPTS 870.3800); OECD 416 in rats.

Dose and Endpoint for Risk Assessment: The NOAEL is 1000 ppm (50 mg/kg/day) from MRID 40276404. The LOAEL is 3000 ppm (150 mg/kg/day) based on decreased F1 and F2 pup weights (6-12%) seen in MRID 44082201, parental toxicity as decreased body weight (4-6%) and increased liver weight in F0 and F1 parental animals, and an increase in absolute and relative spleen weight, and decreased absolute uterine weight in F1 adults and on decreased body weight gain during lactation of F2b pups, and decreased litter size of F1b litters, decreased absolute heart and kidney weight in F2b males, increased relative liver weight in male and female F2b pups seen in both studies.

Comments about Study/Endpoint/Uncertainty Factors: The pup body weight decreases in the reproduction study occurred over a 21 day period (during lactation) which approximates the duration of the short term (1-30 days) scenario. Additionally, the subchronic liver effects, which also had a NOAEL of 50 mg/kg/day, in the parental animals, were observed after about 90-180 days when the rats were sacrificed in the 2-generation study. The parental liver effects were likely initiated during the pup phase of the study during lactation. An uncertainty factor of 100 (10x for interspecies extrapolation, 10x for intraspecies variation is applied for general population excluding children <6 years old. For juvenile susceptibility a 3X uncertainty factor is added for children <6 years old.

A.3.5 Dermal Exposure (Short-, Intermediate- and Long-Term)

D-phenothrin was tested in a 21-day dermal toxicity study in rats (MRID 41009710) at the following dose levels: 0, 100, 300, or 1000 mg/kg/day on the clipped trunk in 5/sex/dose Crl:CD®BR rats. There were no treatment related systemic effects in clinical signs, body weight, food consumption, hematology, clinical chemistry, organ weights or histopathology. Desquamation of the skin in female rats occurred at the following incidence: 2/5, 4/5, 3/5, and 4/5 in controls, low-, mid-, and high-dose groups, respectively. The systemic toxicity NOAEL was 1000 mg/kg/day (HDT). A LOAEL was not established.
Since developmental effects are not measured in the dermal study, the dermal toxicity study may

not be protective of developmental effects. However, the developmental NOAEL of 30 mg/kg/day for spina bifida in the rabbit developmental study, when coupled with the assumption of a conservative dermal absorption factor of 2.0%, results in a dermal NOAEL estimate of 1500 mg/kg/day. This level of exposure significantly exceeds the developmental limit dose (1000 mg/kg/day) and the dermal toxicity study NOAEL of 1000 mg/kg/day. Based on this analysis, neither developmental nor systemic effects from the dermal exposure route are expected at levels well above the limit dose and a dermal endpoint was not selected for this assessment.

A.3.6 Inhalation Exposure (Short-, Intermediate- and Long-Term)

Study Selected: Subchronic Inhalation Study-Rat

MRID No.: 41289201

Executive Summary: In a subchronic inhalation study (MRID 41289201), groups 10 sex/dose Sprague-Dawley rats were exposed by whole body exposure to technical d-phenothrin aerosols at concentrations of 0, 0.030, 0.104, 0.291, or 1.066 mg/L, (0, 7.67, 26.6, 74.4, 272.7 mg/kg) 6 hours/day, 5 days/week for 13 weeks. The mass median aerodynamic diameters (MMAD) of the d-phenothrin aerosol particles ranged from 1.38 to 2.00 μm. There were no effects on survival, body weight, food consumption, and hematologic and clinical chemistry values considered biologically significant in any of the exposure groups. No treatment related gross lesions were observed and ophthalmoscopic examinations were negative. No adverse effects were noted at 0.030 and 0.104 mg/L. A reduced response to knocks on the chamber door during exposure at 1.066 mg/L was the only clinical sign attributed to treatment with the test material. Evidence suggestive of liver toxicity included increased absolute and relative liver weights in males (23% and 25%, respectively) and females (39% and 38%, respectively) associated with centrilobular hepatocyte enlargement and increased thyroid weights (25%) and slight histopathology in the thyroid (minimally increased height of the follicular epithelium of the thyroid) in females were seen at 1.066 mg/L. Also seen were increased absolute adrenal weights (21%) in females at 1.066 mg/L and minor histopathological adrenal lesions in males (cortical vacuolation) at 0.291 and 1.066 mg/L. The histological effects on the liver, thyroid and adrenal are of borderline toxicological significance, but are supported in part by the increased organ weights and histological findings of similar occurrence in some oral studies. Both sexes exhibited an increased incidence and severity of histopathological lesions in the nasal turbinates (eosinophilic inclusions in olfactory epithelial cells at 0.291 and 1.066 mg/L).

The NOAEL is 0.104 mg/L (26.6 mg/kg/day) and the LOAEL is 0.291 mg/L (74.4 mg/kg/day) based on histopathological changes in the nasal turbinates in both sexes. Also present at 1.066 mg/L (272.7 mg/kg/day (HDT)) were increased absolute and relative liver weights in both sexes which were also associated with centrilobular hepatocyte enlargement in females. Increased thyroid weights in females and minimally increased height of the follicular epithelium of the thyroid in females were also observed at 1.066 mg/L. Additionally, increased absolute adrenal weight in females and minimal to moderate cortical vacuolation of the adrenal were seen in males at 0.291 and 1.066 mg/L.

Dose/Endpoint for Risk Assessment: The NOAEL is 0.104 mg/L (26.6 mg/kg/day) and the LOAEL is 0.291 mg/L (74.4 mg/kg/day) based on histopathological changes in the nasal turbinates in both sexes. For HEC and HED calculations, see table 4.5.4.2

Comments about Study/Endpoint: The MOE requirement of 100 for all duration exposure scenarios for inhalation exposed non-workers is based on the conventional uncertainty factor of 100x (10x and 10x for interspecies and intraspecies differences). However, based on the derivation of the human equivalent dose (HED), the animal to human uncertainty factor of 10x is reduced to 3 x which results in a total MOE of 30. For juvenile susceptibility a 3X uncertainty factor is added for children <6 years old.

A.4 Executive Summaries

A.4.1 Subchronic Toxicity

870.3100 90-Day Oral Toxicity – Rat

In a 13-Week oral range-finding toxicity study (MRID 40998202), Sumithrin (92.6% a.i., Lot No. 10102) was administered to Fischer F344 rats 15/sex/dose in the diet at dose levels of 0, 300, 1000, 3000, or 10,000 ppm (equivalent to 0, 21/23, 70/75, 216/227 or 706/714 mg/kg bw/day in males/females).

There were no unscheduled deaths. There were no clinical signs of toxicity.

Possible treatment-related effects were observed at 10,000 ppm compared to controls. Lymphocytes were increased in males and females. Females had increased hydrometra. Liver and liver-related effects included increased liver enzyme activity (males only), decreased cholesterol, increased lactase dehydrogenase, increased plasma albumin, decreased glucose (females only), increased liver weights (both absolute and relative to body weight), and increased biliary hyperplasia (males only). All other examined parameters were similar to those reported for control animals.

Very limited evidence of minor liver toxicity was observed in the 3000 ppm males and females. The noted effects were decreased cholesterol, increased lactase dehydrogenase (females only), decreased glucose and increased liver weights (both absolute and relative to body weight). All other examined parameters were similar to those reported for control animals.

Decreased mean glucose was reported in all treated female groups (300, 1000, 3000, and 10,000 ppm) when compared to concurrent control values. However, inter-group differences were very small and there was no apparent dose-related trend.

The LOAEL is 216 mg/kg/day in males and 227 mg/kg/day in females (3000 ppm), based on increased liver weight, increased lactase dehydrogenase, and decreased cholesterol in both sexes. The NOAEL is 70 mg/kg/day in males and 75 mg/kg/day in females (1000 ppm).

This 13-week oral toxicity study in the rat is acceptable, guideline and satisfies the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in rats.

870.3100 90-Day Oral Toxicity - Mouse

In a 5-week oral toxicity study (MRID 40998201) Sumithrin (92.6% a.i., Lot No. 10102) was administered to B6C3F1 hybrid mice, 12/sex/dose in the diet at dose levels of 0, 300, 1000, 3000, or 10,000 ppm (equivalent to 0, 57/71, 190/230, 565/710, 1958/2339 mg/kg bw/day for males/females, respectively).

There was no treatment-related mortality. There were no treatment-related effects on clinical observations (e.g. appearance and behavior), body weight or body weight gain, or food consumption. Also, no neoplastic lesions were noted. Equivocal effects included increased water consumption during Week 1 (relative to controls) for 10,000 ppm males and females. Increased water consumption remained at Week 5, but only for 10,000 ppm males, and was accompanied by decreased mean kidney weights. Other equivocal effects included increased food conversion ratios over 5 weeks in 10.000 ppm males and females, and a statistically significant hematological effect of decreased mean Packed Cell volume at 10,000 ppm in males and females.

Possible treatment related effects were observed in the liver of both high dose males and females (10,000 ppm), as evidenced by increases in alkaline phosphatase activity, increased liver weights (both absolute and relative to body weight), and increased periacinar hepatocytic hypertrophy when compared to control animals. In addition, decreased kidney weights (absolute and relative to body weight) were also observed in high dose males, and may be indicative of a toxic response.

An increase in liver weights (both absolute and relative to body weight), and periacinar hepatocytic hypertrophy was observed in the next highest dose (3000 ppm) males, while an increased in liver weights only was reported in females of this group when compared to respective control animals; no differences in other examined parameters were noted.

The LOAEL is 565 mg/kg/day for males and 710 mg/kg/day for females (3000 ppm), based on increased liver weights and increased periacinar hepatocytic hypertrophy (in males only). The NOAEL is 190 mg/kg/day for males and 230 mg/kg/day for females (1000 ppm).

This 5-week oral toxicity range-finding study in mice is acceptable, guideline and does satisfy the guideline requirement for a 28-day repeated dose oral toxicity study (OPPTS 870.3050; OECD 407) in mice. NOTE: OPP does not have a requirement for this guideline and this study does not satisfy the guideline requirement (OPPTS 870.3100) for a 90-day subchronic rat study.

870.3150 90-Day Oral Toxicity - Dog

In a 90-day oral toxicity study (MRID 00148558), Sumithrin (93.1% a.i., Lot 00218 and 95.5% a.i., Lot 91137) was administered to 6 purebred beagle dogs sex/dose in the diet at dose levels of 0 (control), 100, 300, or 1000 ppm (equivalent to 0, 3.02, 9.28, and 31.87 mg/kg bw/day for males and0, 3.14, 9.31, and 32.90 mg/kg bw/day for females). Animals were sacrificed after 26 weeks.

There were no unscheduled deaths. There were no behavioral or clinical signs (e.g. emesis, altered defecation, coat appearance) of toxicity. There were no compound related effects on ophthalmology, hematology, urinalysis, gross pathology, histopathology, or food consumption. There were slight decreases in body weight gain for the males (↓12%) and females (↓25%) in the 1000 ppm groups. Evidence was insufficient that these decreases were due to the test material. Significant (~↑19%) increases in serum alkaline phosphatase were observed in males and females at 1000 pm. However, this is not considered adverse, given the range of control values and the lack of microscopic effects. Increases in relative and absolute liver weights were observed in males at 1000 ppm only.

A LOAEL was not determined. The NOAEL is 31.87 mg/kg bw/day for males and 32.90 mg/kg bw/day for females (1000 ppm).

This 26-week oral toxicity study in the dog is classified acceptable, guideline and satisfies the guideline requirement for a subchronic oral toxicity study (OPPTS 870.3150; OECD 409) in dogs.

870.3200 21/28-Day Dermal Toxicity – Rat

No study available.

870.3465 90-Day Inhalation – Rat. See A.3.6. above

A.4.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study - Rat

In a developmental toxicity study (MRIDs 00153471, 47452201) Sumithrin (92.6% a.i., Lot No. 10102) was administered to 20 pregnant CD rats/dose by gavage (in corn oil) at dose levels of 0, 300, 1000, or 3000 mg/kg bw/day from days 6 through 15 of gestation (GD 6-15). Animals were sacrificed on GD 21.

There were no maternal deaths or abortions. Significant ($p<0.001$) decreases in maternal weight gain (uncorrected for gravid uterine weights) were observed during the treatment period (Days 6-16) at 3000 mg/kg bw/day (37± 24 g compared to 62 ± 12 g in controls). Maternal weight gain was also decreased ($p<0.05$) over the treatment/post-treatment period at this dose (111 ± 32 g compared to 128 ± 21 g in controls). This was accompanied by a significant decrease in food consumption over the treatment period. Water intake was significantly increased throughout the treatment and post-treatment period at 3000 mg/kg bw/day, and also at 1000 mg/kg bw/day, with the exception of treatment days 9-11. These effects are not considered to indicative of possible adverse human health effects since they occur above the limit test of 1000 mg/kg bw/day.

The maternal LOAEL is 3000 mg/kg bw/day, based on decreased weight gain and food consumption and increased water consumption. The maternal NOAEL is 1000 mg/kg bw/day.

At 3000 mg/kg bw/day, statistically significant differences were observed in fetal body weights, placental weights, and the incidence of small fetuses. Fetal body weights were significantly decreased in 3000 mg/kg bw/day animals (3.18 ± 0.08 g) compared to controls (3.46 ± 0.08 g), while mean placental weights were increased to 0.53 ± 0.02 compared to 0.47 ± 0.02 for controls. The incidence of small (<2.7 g) fetuses was increased to 13.5 in 10 litters compared to 1.8 fetuses in 4 litters for controls. No statistically significant increases in cesarean parameters or malformations were observed at or below the limit dose of 1000 mg/kg bw/day.

The developmental LOAEL is 3000 mg/kg bw/day, based on decreased fetal body weight, increased placental weight, and increased incidence of small fetuses. The developmental NOAEL is 1000 mg/kg bw/day.

This developmental toxicity study in the rat is classified as acceptable, guideline; and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

MRID 41230003. SeeA.3.1. above

MRID 49173605

This non-guideline developmental toxicity study (MRID 49173605) was conducted to confirm hydrocephalus observed in fetuses in a previous study with Sumithrin (MRID 41230003). Therefore, Sumithrin (96.8% a.i., batch/lot # 080506) in a 0.5% methylcellulose vehicle at a dose of 750 mg/kg bw/day was administered by gavage to a group of 60 timed-mated New Zealand White [Hra:(NZW)SPF] female rabbits from gestation days (GDs) 6 to 28 inclusive. A group of 23 time-mated female rabbits was similarly dosed with the vehicle. The test substance was administered in 0.5% methylcellulose. The test material and vehicle were administered in a volume of 5 mL/kg. The does were sacrificed on GD 29 for evaluation of maternal and developmental parameters. Fetuses were weighed, sexed, and examined for external abnormalities. The heads were examined in about one-half the fetuses by a cross-section between the parietal and frontal bones and the brain examined *in situ*. All fetuses were eviscerated, cleared, stained with Alizarin red S and examined for skeletal alterations.

Eight does of the sumithrin group did not survive to study termination: two dams were found dead (GDs 14 and 20), two were sacrificed because of adverse clinical observations (GDs 18 and

20), and four were sacrificed following abortion (GDs 18, 21, 21, and 26). All had severely reduced weight gain and food consumption prior to death, and all were pregnant. The deaths and abortions may have been secondary to severely decreased food consumption and decreased weight gain. Treatment-related clinical signs were primarily scant or no feces, soft or liquid feces, ungroomed coat, thin body condition, and dehydration. Mean absolute body weights of the 750-mg/kg/day group were similar to those of controls throughout the study. A transient weight loss was observed from GD 6 to 9 (-0.13 kg vs 0.00 kg for controls, $p \leq 0.01$) and from GD 9 to 12 (0.03 kg vs 0.00 for controls, N.S.) intervals; treated does lost 0.17 kg over the GD 6 to 12 interval, whereas controls gained 0.1 kg. Overall weight gain in the 750-mg/kg/day group was 36% ($p \leq 0.05$) less than that of controls from GD 6 to 29. Corrected body weight and weight gain was similar in the treated and control groups. A transient decrease in food consumption was observed in the 750-mg/kg/day group compared with that of controls. Treated does consumed -34% ($p \leq 0.01$) less food than controls from GDs 6 to 9, -36% to -37% less ($p \leq 0.01$) from GDs 9-12, and -21% to -22% less (N.S.) from GD 12 to15 whether calculated as g/doe/day or g/kg bw/day. Overall food consumption from GD 6 to 29 was similar to that of controls. No test substance-related gross lesions were observed in does administered the 750-mg/kg/day dosage.

Oral administration of Sumithrin to pregnant rabbits at 750 mg/kg bw/day from GD 6-28 resulted in adverse clinical signs (scant or no feces, soft or liquid feces, ungroomed coat, thin body condition, and dehydration), and transient decreases in body weight gain and food consumption. Deaths and abortions were also seen at the only dose tested.

No dead fetuses were found at cesarean section of does administered the test substance and the sex ratio was similar in the treated and control groups. The number of resorptions (total number, percent resorptions/doe or litter, total number of early resorptions, early resorptions/doe) and postimplantation losses were significantly increased in the treated group compared with that of concurrent controls, but were within range of historical controls and are not considered treatment related. No treatment-related effect was observed on male, female, or the combined male/female fetal weights. No treatment-related effect was observed on external, visceral, or skeletal malformations or variations. There were no effects on skeletal ossification or the average number of ossification sites attributed to treatment with the test substance. Misaligned caudal vertebrae observed in five fetuses in four litters in the 750-mg/kg/day group compared with none of the controls were within range of historical controls and are not considered test substance related.

This study showed no test substance-related effects on fetal deaths, fetal growth, or developmental malformations or variations, and specifically no treatment-related hydrocephalus was observed among 367 fetuses in 48 litters.

The developmental toxicity study in the rabbit is classified **Acceptable/Non-guideline** and satisfied the purpose of confirming that hydrocephalus observed in a previous study (MRID 41230003) with Sumithrin should not be attributed to the test substance.

A.4.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects – Rat-See 3.4.1

I deleted these here because it is repetition of 3.4.1 above

A.4.4 Chronic Toxicity

870.4100a (870.4300) Chronic Toxicity – Rat

See below

870.4100b Chronic Toxicity – Dog. MRID 40276401 See A.3.3 above

A.4.5 Carcinogenicity

870.4200a Carcinogenicity Study - rat

In a combined chronic toxicity / carcinogenicity study (MRID 40276405) Sumithrin (92.6% a.i., Lot Not. 10102) was administered to specified pathogen-free, F344 rats 50 sex/dose in the diet at dose levels of 0, 300, 1000, or 3000 ppm (equivalent to 0, 15, 50, 150 mg/kg bw/day) for 106-108 weeks (males) or 119-121 weeks (females).

The percentage of males that survived to termination at 108 weeks was 24-54%, while 30-52% of females survived to termination at 121 weeks. However, the test material had no effect on the distribution or time of deaths (i.e. there was no treatment-related mortality). There were no clinical signs of toxicity and no effects on ophthalmology. No compound-related effects on hematology, clinical chemistry, or urinalysis were observed. For males, there were no treatment-related effects on body weight or body weight gain, but for females, small (up to 6.5%) but statistically significant decreases in body weight gain were seen at 1000 and 3000 ppm. There were no effects of the test material on food and water consumption or food conversion ratios. For females, a relative (to body weight) increase in liver weights was observed at 52 weeks, and absent at terminal sacrifice, while for males, a relative increase in liver weight was not observed at 52 weeks but was present at terminal sacrifice.

The LOAEL is 150 mg/kg/day (3000 ppm), based on <u>slightly</u> decreased body weight gain in females, increased relative liver/body weight ratios in males, increased cystic dilation of sinuses in mesenteric lymph nodes in males, and increased periacinar hepatocytic hypertrophy of the liver in males. The NOAEL is 50 mg/kg/day (1000 ppm).

At the doses tested, there was not a treatment related increase in tumor incidence. However, there was a significant increase in the incidence of non-neoplastic lesions in males only at 3000 ppm. These were cystic dilation of the sinuses in the mesenteric lymph nodes (15/45 in treated versus 2/47 in controls) and periacinar hepatocytic hypertrophy in the liver (7/50 in treated versus 0/50 in controls). Dosing was not considered adequate based on a lack of clear toxicity in the high dose groups, and (below) the registrant is requested to justify the dosage in relation to the maximum tolerated dose.

This chronic toxicity /carcinogenicity study in the rat is **unacceptable/guideline** and **does not satisfy** the guideline requirement for a chronic toxicity / carcinogenicity study OPPTS 870.4300); OECD 453] in rats.

870.4200a Carcinogenicity Study – rat

In a combined chronic toxicity / carcinogenicity study (MRID43927001), Sumithrin (94% a.i., Lot #10914) was administered to F-344 rats, 50/sex/dose in the diet at dose levels of 0, 1000, 10,000 or 20,000 ppm (equivalent to 0, 51, 531 and 1116 mg/kg bw/day in males and 0, 63, 653 and 1351mg/kg bw/day in females) for two years for the oncogenic segment. For the chronic segment (which was not examined histologically) 20 rats/sex were administered the same dosing regimen. An additional 10 rats/sex/group were similarly treated and sacrificed at 12 months.

Detailed statistical analysis of mortality was performed (TXR 0054109) and there were no treatment-related trends or differences for females. Male rats showed a statistically significant *decreasing* trend for mortality, as well as negative pair-wise comparisons of the 10,000 and 20,000 ppm dose groups with the controls, all at $p<0.01$.

Males and females in the 20,000 ppm group and females in the 10,000 ppm group appeared thin, had a hunched posture and had yellow/urinary staining of the perigenital area. Hemorrhage was the major clinical sign of toxicity observed between weeks 64-68. Body weight gain was decreased in males and females in the 10,000 and 20,000 ppm groups (60-80% of control values) during weeks 0-64 (males) and weeks 0-94 (females). Food consumption was decreased at 20,000 ppm (6-13%) and food efficiency was decreased at 10,000 and 20,000 ppm (8-20%). Posterior capsular opacity was increased in females in the 10,000 and 20,000 ppm groups. Mild anemia was apparent in animals in the 10,000 and 20,000 ppm groups based on decreases in HCT, HGB and RBCs. Fibrinogen levels were also decreased in the 10,000 and 20,000 ppm groups. Several serum enzymes (leucine amino peptidase, alkaline phosphatase and GGT) were elevated in males and/or females in the 10,000 and 20,000 ppm groups. Triglyceride and phospholipid levels were decreased in males and females in the 10,000 and 20,000 ppm groups. Total protein was decreased at 20,000 ppm. Alpha-1 and Alpha 2 globulin were decreased in the 20,000 ppm group and Alpha-2 globulin was decreased in females in the 10,000 ppm group. The ratio of alpha globulins 1 and 2 to beta globulin (A/G ratio) was significantly increased in the 10,000 and 20,000 ppm groups. A decrease in specific gravity and pH of the urine was noted in animals in the 10,000 and 20,000 ppm groups. Absolute and/or relative liver weights were increased in animals in the 10,000 and 20,000 ppm groups. At necropsy animals in the 20,000 ppm group and females in the 10,000 ppm group appeared thin. Males in the 20,000 ppm group had a greater incidence of subcapsular fluid in the testes. Panacinar hypertrophy was observed in animals in the 10,000 (22-28%) and 20,000 (80-84%) ppm groups compared to controls (0%). Congestion of the liver was also observed in animals in the 20,000 ppm group (14-26%) compared to controls (4-6%). Hepatocellular carcinoma and hepatocellular adenoma and carcinoma combined were increased in males and females in the 20,000 ppm group.

The LOAEL is 10,000 ppm (531 mg/kg bw/day in males and 653 mg/kg bw/day in females) based on clinical signs of toxicity, decreases in body weight gain, food efficiency, triglycerides, phospholipids, α-2 globulin, urinary pH and specific gravity, and increases in serum enzymes, A/G ratio, posterior capsular opacity, liver weights and liver pathology. The NOAEL is 1000 ppm (51 mg/kg bw/day in males and 63 mg/kg bw/day in females).

The test material induced hepatocellular tumors in rats at doses that caused excessive toxicity. Male rats had statistically significant trends for liver adenomas, carcinomas, and adenomas and/or carcinomas combined, all at $p<0.01$. There were statistically significant pair-wise comparisons of the 20,000 ppm dose group with the controls for liver carcinomas and adenomas and/or carcinomas combined, both at $p<0.05$. Female rats had statistically significant trends, and statistically significant pair-wise comparisons of the 20,000 ppm dose group with the controls, for liver carcinomas and adenomas and/or carcinomas combined, all at $p<0.01$.

This chronic toxicity /carcinogenicity study in rats is acceptable, guideline and satisfies the guideline requirement for a chronic toxicity / carcinogenicity study (OPPTS 870.4300; OECD 453) in rats.

870.4200b Carcinogenicity (feeding) - Mouse

In a combined chronic toxicity /carcinogenicity study (MRIDs 40276402, 41289705, 41289701, 41289702) Sumithrin (92.9% a.i., Lot No. 21005) was administered to B6C3F1 hybrid strain mice in the diet at dose levels of 0, 300, 1000, or 3000 ppm (equivalent to 0, 45, 150, or 450 mg/kg bw/day) for Lifespan and Toxicity studies. Lifespan studies fed Sumithrin to 50/sex/dose for 105 weeks (males) or 106 weeks (females). Toxicity studies fed Sumithrin to 40/sex/dose. Ten animals/sex/dose were sacrificed at 26, 53, and 78 weeks with the remaining survivors sacrificed at 78 weeks.

Detailed statistical analyses of changes in mortality were provided (TXR 0054109), but no significant, dose-dependent differences were found in male or female mice. Also, there were no compound-related effects on ophthalmological examinations, hematology, clinical chemistry, or urinalysis. Increased liver weights were observed in male mice at 1000 and 3000 ppm and in female mice at 3000 ppm. Decreased kidney weights were observed in male mice at 1000 ppm and 3000 ppm, while kidney weights were increased in females at 3000 ppm.

Slight effects of Sumithrin on body weight changes were investigated by two different statistical methods. The student's t-test (MRID 41289701) showed that body weight and body weight gain in males were generally statistically significantly less ($p<0.05$, $p<0.01$, $p<0.001$) in the 3000 ppm group compared with the controls over the first 60 weeks of treatment. Body weight and body weight gain of female mice at 3000 ppm were generally similar to controls for the first 52 weeks of treatment and only became statistically significant in weeks 76 to 84 out of 104 weeks. Multivariate analysis (MRID 41289702) showed that the rate of growth for the sumithrin-treated males, particularly the 3000 ppm group, was significantly less than the controls during weeks 0-78. In females, the results were less clearly defined. There was a slight decreased in growth rate in the 3000 ppm group during the lifespan and toxicity phases, but there was no corresponding effect in both phases of growth, when compared together, for the 300 and 1000 ppm female groups.

The LOAEL is 150 mg/kg bw/day for males (1000 ppm), based on increased liver weights and decreased kidney weights. The NOAEL is 45 mg/kg bw/day (300 ppm). The LOAEL for females is 450 mg/kg bw/day (3000 ppm), based on slight decreases in body weight gain, increased liver weights, and increased kidney weights. The NOAEL is 150 mg/kg bw/day (1000 ppm).

Detailed statistical analysis of tumor incidence was provided (TXR 0054109). For liver adenomas, male mice had a statistically significant trend, and statistically significant pair-wise comparisons of the 1000 and 3000 ppm dose groups with controls, all at $p<0.05$. There was also a statistically significant pair-wise comparison of the 1000 ppm dose group with the controls for liver adenomas and/or carcinomas combined at $p<0.05$. The incidence of historical control data for adenomas in male mice was 12-40% for six studies from the UK laboratory. This range is slightly less than occurrence of 42% adenomas in the 1000 and 3000 ppm groups. Additionally, the combined incidence of 26-50% in the historical controls is exceeded by the occurrence of the combined incidence of 62% at the 1000 ppm dose level. No significant trends for mouse liver tumors were observed for females. However, there was a significant increase in adenomas and/or carcinomas combined at 3000 pm compared to controls ($p<0.05$). The combined incidence of 30% in the 3000 ppm dose level is within the range of 2-32% combined incidence in the female historical controls. However, since the mouse liver tumors are a common tumor in B6C3F1 mice, the use of a statistical significance of $p<0.01$ is needed for support of carcinogenicity. The CARC (May 30, 2006) determined that the liver tumors in B6C3F1 mice are not treatment-related.

At the doses tested, there was not a treatment related increase in liver tumor incidence (adenoma/carcinoma) when compared to controls. The CARC determined that although the mice could have tolerated higher doses, dosing was considered adequate because the HDT of 3000 ppm was ½ the limit dose for a mouse carcinogenicity study.

This chronic/carcinogenicity study in the mouse is classified acceptable, guideline and satisfies the guideline requirement for a chronic/carcinogenicity study OPPTS 870.4300); OECD 453] in mice.

A.4.6 Mutagenicity

Gene Mutation

870.5100, Gene Mutation MRID 00148559 Acceptable/guideline	D-phenothrin was not mutagenic both with and without metabolic activation (S-9) in Salmonella typhimurium strains TA 98, TA100, TA1535, TA1537, TA1538 and E. coli WP-2uvrA gene mutation

Cytogenetics

870.5375 *in vitro* chromosome Chinese hamster ovary (CHO) cell assay. MRID 41009711 Acceptable/guideline	Negative for inducing chromosome aberrations in CHO cells exposed with and without S-9 up to cytotoxic or precipitating dose levels
870.5375 *in vitro* chromosome Chinese hamster ovary (CHO) cell assay. MRID 00160488 Acceptable/guideline	Negative for inducing chromosome aberrations in CHO cells exposed both with and without metabolic activation (S-9) up to cytotoxic or precipitating dose levels
870.5395 *in vivo* mouse cytogenetic assay MRID 00148561 Acceptable/guideline	No clastogenic response in bone marrow of male mice administered a single intraperitoneal injection up to a level (10,000 mg/kg) which was well above the limit dose of 2,000 mg/kg
In vitro DNA damage in in human peripheral blood lymphocytes and in human hepatocytes Nagy *et al* (2014)* Acceptable/non-guideline	D-phenothrin induced statistically significant, dose-dependent DNA damage in the absence of marked cytotoxicity at concentrations higher than 20 µM and 50 µM in human blood peripheral lymphocytes and hepatocytes, respectively. Oxidative DNA damage could also be detected in the two cell types, although this did not reach statistical significance.

Other Genotoxicity

Other Effects 870.5550 *in vitro* unscheduled DNA synthesis (UDS) MRID 00160489 Acceptable/guideline	Did not induce significant increases in UDS in HeLa cells up to 4000 µg/ml.

A.4.7 Neurotoxicity

870.6200 Acute Neurotoxicity Screening Battery

n an acute neurotoxicity study (MRID 47593101), groups of non-fasted Wistar rats (10/sex/dose) were given a single oral (gavage; 5 mL/kg) dose of Sumithrin (97% a.i., Batch # 070504G) in corn oil at doses of 0, 200, 600, or 2000 mg/kg (limit dose) and observed for 14 days. A functional observational battery (FOB) and motor activity testing were performed on all animals during pre-exposure, Day 1 (at 3 hours post-dosing, the estimated time-of-peak effect), and Days 7 and 14. At study termination, 5 animals/sex/group were euthanized and perfused *in situ* for neuropathological examination. The brain and peripheral nervous system tissues collected from the perfused animals in the control and 2000 mg/kg groups were subjected to histopathological evaluation. Positive control data were provided (MRID 47803001).

No compound-related effects on mortality, clinical signs of toxicity, body weight, body weight gain, food consumption, FOB parameters, motor activity, absolute or relative (to body) brain weight, or gross or neuropathology were observed at any dose in either sex.

The neurotoxicity LOAEL was not observed. The neurotoxicity NOAEL is 2000 mg/kg (limit dose).

This study is classified as **Acceptable Guideline** and satisfies the guideline requirement (870.6200a; OECD 424) for an acute neurotoxicity study in rats.

870.6200 Subchronic Neurotoxicity Screening Battery

In an subchronic neurotoxicity study (MRID 49173604), five groups of HanRcc:WIST(SPF) rats (10/sex/group; ~6 weeks of age) were administered 0, 1000, 3000, 10,000, or 20,000 ppm of d-phenothrin [96.8% (Batch No. 080506)] in the diet and observed for 92 days. The respective dose levels based on food consumption were 0**,** 72.9, 208.2, 726.9, and 1456.0 mg/kg bw/day for males and 0, 75.9, 230.3, 738.6, and 1502.1 mg/kg bw/day for females. Clinical examinations were conducted weekly, and a neurobehavioral assessment [functional observational battery (FOB) and motor activity (MA) testing] were performed on all rats during weeks -1, 2, 5, 9, and 13. At study termination, 5 rats/group/sex were euthanized and perfused *in situ,* tissues collected for possible neuropathological examination, and brain weights were measured. The tissues collected from 5 rats/sex from the control and high dose groups were examined microscopically.

There were no mortalities or toxicologically significant clinical observations at any dietary concentration of d-phenothrin. Statistically lower ($p \leq 0.01$) body weight and body weight gain were observed in females at the high dose throughout the experimental period. A transient decreased body weight gain was observed in males at the high dose during days 5-12 ($p \leq 0.05$). Body weight gain in females at the mid-high dietary concentration (10,000 ppm) was statistically lower beginning on day 5 and continuing throughout the experimental period. Food consumption was lower in females (typically $p \leq 0.01$) at the high dose during weeks 1-4, and in females at the mid-high concentration during weeks 3 and 4. Several sporadic findings in FOB results were statistically significant but were not considered test substance-related since the incidences were transient, too low to be toxicologically significant and/or there was no dose-response relationship. No statistically significant findings in total counts were observed in males or females during any of the testing sessions except for one total vertical count (rearing) during the pre-test session. There were no treatment-related findings during ophthalmoscopic examinations or during the gross examination of rats. Statistically higher relative brain weight ($p \leq 0.05$) was observed in the high-dose females (0.99 vs. 0.86 in controls). This difference was attributed to the statistically lower terminal body weight in this group. There were no test substance-related or other remarkable findings in the microscopic examination of neurological tissues.

Based on the body weight effects seen in this study, the systemic toxicity LOAEL for d-phenothrin in the diet was 20,000 ppm for males (equivalent to 1456.0 mg/kg bw/day), and 10,000 ppm for females (equivalent to 738.6 mg/kg bw/day) for subchronic neurotoxicity in rats. The NOAEL was 10,000 ppm for males (equivalent to 726.9 mg/kg bw/day), and 3000 ppm for females (equivalent to 230.3 mg/kg bw/day). No adverse effects in the neurotoxic measures were reported at the highest dose tested.

This neurotoxicity study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for subchronic neurotoxicity study in rats (OCSPP 870.6200; OECD 424).

870.6300 Developmental Neurotoxicity Study

The Agency has reviewed existing pyrethroid DNT data for six pyrethroids in 2010 (D371723, 1/20/10, TXR 0055306) and concluded that the DNT is not a particularly sensitive study for comparing the sensitivity of young and adult animals to pyrethroids. Additionally, the degree of concern for these effects in infants is low because the rat reproductive and offspring effects have clearly defined NOAEL/LOAELs and the POD selected for risk assessment is protective of these effects. Based on this review a DNT study is not required for d-phenothrin.

A.4.8 Metabolism

870.7485 Metabolism - Rat

In a metabolism study (MRID 40276403) [^{14}C]-d-phenothrin (label at the benzyl ^{14}C, no radiochemical purity data or lot numbers available) was administered to Sprague Dawley rats 5 sex/dose in corn oil by gavage in a single oral dose at dose levels of 0, 4, or 200 mg/kg bw in cis or trans [^{14}C]-d-phenothrin. Repeated dose studies similarly dosed 5/sex/dose at 4 mg/kg bw once a day for 14 days with unlabeled cis or trans d-phenothrin. Twenty-four hours later, the rats were dosed with 4 mg/kg radiolabeled cis or trans d-phenothrin.

Nearly 96 to 100% of [^{14}C]-Sumithrin was eliminated in the urine and feces within 7 days. Of the low amounts in tissues, the cis isomer was present at 2 to 10-fold greater levels in fat than the trans isomer. In addition to fat, the skin with hair and the carcass also had low amounts of radioactivity.

There were few differences between sexes in the amount of [^{14}C] excreta, in tissues, or in amounts and identity of metabolites in excreta for the low dose and high dose groups. The repeated dose groups had higher levels of urinary metabolites indicating improved absorption.

The major urinary metabolite was 3-(4-hydroxyphenoxy) benzoic acid sulfate (4'-OH-PB acid sulfate) which was present at levels ranging from 6.8 to 17.9% for the cis isomer and from 14.8-55.4% for the trans isomer.

There were no apparent significant sex differences between [^{14}C]-excreta, [^{14}C]-tissue residues and amounts and identity of metabolites.

The major metabolic pathway proposed based on the data involves hydrolysis of the ester linkage, followed by conjugation with glucuronic acid, glycine, or sulfuric acid.

This metabolism study is classified as acceptable, guideline and satisfies the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats.

870.7600 Dermal Absorption - Rat

No dermal absorption study conducted with d-phenothrin, but based on a study conducted with pyrethrin in humans (46382501), pyrethroids have a low absorption value of ≤ 5% and a high rate of metabolism. This is typical of the pyrethroids, as they are lipophilic, and much of the radioactivity measured in the skin of dermal penetration studies with pyrethroids is captured in the upper dermal layers and not available for absorption or systemic circulation.

A.4.9 Immunotoxicity

870.7800 Immunotoxicity

Study was waived (TXR: 0056770 and HASPOC TXR: 0056729)

Appendix B. Physical/Chemical Properties

TABLE 3.1. Physicochemical Properties of the Technical Grade Test Compound: D-phenothrin.

Parameter	**Value**	**Reference**
Melting point/range	Not applicable; TGAI is a liquid	
pH	5.16 at 20 °C	MRID 41009702; DP Barcode D202482, 11/5/02, T. Morton
Density	1.060 specific gravity at 20 °C	
Water solubility	<9.7 µg/L at 25 °C	MRIDs 41009704 and 41009705; DP Barcode D202482, 11/5/02, T. Morton
Solvent solubility	>4.96 g/mL in hexane at 25 °C >5.0 g/mL in methanol at 25 °C	
Vapor pressure	1.04 x 10^{-7} mm Hg at 21 °C	MRID 41009707; DP Barcode D202482, 11/5/02, T. Morton
Dissociation constant, pK_a	Not available	
Octanol/water partition coefficient, $Log(K_{OW})$	log P_{ow} = 6.76 at 25 °C log P_{ow} = 6.01 at 20 °C	MRIDs 41009704 and 41009706; DP Barcode D202482, 11/5/02, T. Morton
UV/visible absorption spectrum	Not available	

Appendix C. Summary of US and International Tolerances and Maximum Residue Limits

<table>
<tr><td colspan="5">Summary of US and International Tolerances and Maximum Residue Limits for d-phenothrin (PC Code 069005; Date of Request 1/19/16)</td></tr>
<tr><td colspan="5">Residue Definition:</td></tr>
<tr><td colspan="2">US</td><td>Canada</td><td>Mexico[1]</td><td>Codex</td></tr>
<tr><td colspan="2">40 CFR: 180.647
d-phenothrin</td><td>None</td><td></td><td>None</td></tr>
<tr><td rowspan="2">Commodity</td><td colspan="4">Tolerance (ppm) /Maximum Residue Limit (mg/kg)</td></tr>
<tr><td>US</td><td>Canada</td><td>Mexico[1]</td><td>Codex</td></tr>
<tr><td>Residues of the insecticide d-phenothrin in or on all food/feed crops following wide-area mosquito adulticide applications</td><td>0.01 ppm</td><td></td><td></td><td></td></tr>
<tr><td colspan="5">Completed: M. Negussie; 01/20/16</td></tr>
</table>

[1] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

Appendix D: Human Equivalent Dose (HED) Calculations for the Inhalation Risk Assessment

Sub-chronic Inhalation Study in Rats (MRID 41289201

NOAEC = 0.104 mg/L or 104 mg/m^3

LOAEC= 0.291 mg/L or 291 mg/ m^3 based on histopathological changes in the nasal turbinates in both sexes.

Mass Median Aerodynamic Diameter (MMAD) = 1.47

Geometric Standard Deviation (GSD) = 1.80

Calculated Regional Deposited Dose Ratio (RDDR) = 0.186 (female rats)

The mass median aerodynamic diameters (MMAD) of the d-phenothrin aerosol particles ranged from 1.38 to 2.00 µm. The particle size of 1.47 µm selected for calculating the RDDR came from the mid dose group where the LOAEC occurred. Geometric Standard Deviation (GSD) was not given in the report, so a default value of 1.80 was used. A body weight of 267 g and 204 g was used for male and female rats. A 70 kg body weight for humans was used. The RDDR are calculated for each region of the respiratory tract and for systemic toxicity (labeled "extrarespiratory"). The effects observed at the LOAEC in the sub-chronic rat study were histopathological changes in the nasal turbinates in both sexes and were considered extrathoracic. Therefore, the extrathoracic RDDR was selected to calculate the HEC and, where appropriate, HED for each anticipated inhalation exposure scenario. The calculations for exposure scenario are detailed below.

Table D.1. Human Equivalent Concentrations and Human Equivalent Dose based on Inhalation Study MRID 41289201 and RRDR Methodology: D-phenothrin

Population	Scenario	Tox duration adjustment		HEC		HED (mg/kg-day)
		hr/day	day/wk	mg/L	mg/m^3	
Occupational	Handler	8	5	0.015	14.508	1.373
Residential	Handler	NA	NA	0.019	19.344	0.458
	Outdoor post-application	NA	NA	0.019	19.344	0.526
	Indoor Post-application	NA	7	0.014	13.817	0.327
	Bystander	24	7	0.003	3.454	NA

Regional deposited dose ratios: SD male rats

MMAD = 1.47
Sigma g = 1.80

SPECIES	Body weight(g)	Extrathoracic VE(ml)	Extrathoracic SA(cm^2)	Extrathoracic dep	Tracheobronchial SA(cm^2)	Tracheobronchial dep	Pulmonary SA(m^2)	Pulmonary dep
rat	**267**	189.8	15.000	0.381	22.500	0.068	0.340	0.073
human	70000	13800.0	200.000	0.258	3200.000	0.065	54.000	0.274
RATIO	0.004	0.014	0.075	1.476	0.007	1.053	0.006	0.265
RDDR			**0.271**		**2.059**		**0.579**	

SPECIES	Thoracic SA(m^2)	Thoracic dep	Total RT SA(m^2)	Total RT dep	Extrarespiratory BW(g)	Extrarespiratory dep
rat	0.342	0.141	0.344	0.522	267	0.522
human	54.320	0.125	54.340	0.597	70000	0.597
RATIO	0.006	1.126	0.006	0.874	0.004	0.874
RDDR	**0.909**		**1.900**		**3.152**	

Regional deposited dose ratios; SD female rats

MMAD = 1.47
Sigma g = 1.80

SPECIES	Body weight(g)	VE(ml)	Extrathoracic SA(cm^2)	dep	Tracheobronchial SA(cm^2)	dep	Pulmonary SA(m^2)	dep
rat	**204**	152.2	15.000	0.326	22.500	0.079	0.340	0.091
human	70000	13800.0	200.000	0.258	3200.000	0.065	54.000	0.274
RATIO	0.003	0.011	0.075	1.263	0.007	1.215	0.006	0.333
RDDR			**0.186**		**1.906**		**0.583**	

	Thoracic SA(m^2)	dep	Total RT SA(m^2)	dep	Extrarespiratory BW(g)	dep
rat	0.342	0.170	0.344	0.496	204	0.496
human	54.320	0.125	54.340	0.597	70000	0.597
RATIO	0.006	1.359	0.006	0.831	0.003	0.831
RDDR	**0.879**		**1.448**		**3.144**	

Occupational Handler:

$NOAEC_{adjusted}$ = 0.104 mg/L * (6 hr/day ÷ 8 hr/day) * (5 days/wk ÷ 5 days/wk) = 0.078 mg/L

HEC (mg/L) = $NOAEC_{adjusted}$ (mg/L) * RDDR = **0.0145 mg/L**

HED (mg/kg/day) = HEC (mg/L) * CF (L/hr-kg) * D (hrs) = **1.37 mg/kg/day**

HEC = 0.0145 mg/L

Human specific conversion factor (CF) = 11.8 l/hr-kg

Duration (D) = 8 hours

Residential Handler:

HEC (mg/L) = NOAEC (mg/L) * RDDR = **0.0.019 mg/L**

HED (mg/kg/day) = HEC (mg/L) * CF (L/hr-kg) * D (hrs) = **0.46 mg/kg/day**

HEC = 0.019 mg/L

CF = 11.8 l/hr-kg

D = 2 hours

Residential Outdoor Post-Application:

HEC (mg/L) = NOAEC (mg/L) * RDDR = **0.019 mg/L**

HED (mg/kg/day) = HEC (mg/L) * CF (L/hr-kg) * D (hrs) = **0.53 mg/kg/day**

HEC = 0.019 mg/L

CF = 11.8 l/hr-kg

D = 2.3 hours

Residential Indoor Post-Application:

$NOAEC_{adjusted}$ = 0.104 mg/L * (5 days/wk ÷ 7 days/wk) = 0.0743 mg/L

HEC (mg/L) = $NOAEC_{adjusted}$ (mg/L) * RDDR = **0.014 mg/L**

HED (mg/kg/day) = HEC (mg/L) * CF (L/hr-kg) * D (hrs) = **0.33 mg/kg/day**

HEC = 0.014 mg/L

CF = 11.8 l/hr-kg

D = 2 hours

Residential Bystander:

$NOAEC_{adjusted}$ = 0.104 mg/L * (6 hr/day ÷ 24 hr/day) * (5 days/wk ÷ 7 days/wk) = 0.019 mg/L

HEC (mg/L) = $NOAEC_{adjusted}$ (mg/L) * RDDR = **0.003 mg/L**